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VOLUME 61
1938

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL

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VOLUME 61

JANUARY 1938

NUMBER 1

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PULMONARY ARTERIOLAR SCLEROSIS

A CLINICOPATHOLOGIC STUDY

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In the past few years disturbances of the pulmonary circulation have been studied with renewed interest, and the term pulmonary hypertension has gained more universal usage. The relative obscurity to which the pulmonary arterial tree has been relegated can be attributed to the following causes: (1) its inaccessibility during life, (2) the lack of accurate anatomic criteria whereby pathologic changes in the different parts of the pulmonary arterial tree can be correctly evaluated at necropsy and (3) the similarity of the clinical manifestations of diseases of the pulmonary arterial tree to those of cardiac diseases and pulmonary disturbances.

The name Ayerza's disease is closely linked with diseases of the pulmonary artery. This term has had an interesting influence on the conception of diseases of the pulmonary artery. According to Brenner,¹ in the case originally discussed by Ayerza, in which the patient was described as a black "cardiac," necropsy disclosed dilatation of the bronchi, peribronchitis and hypertrophy and dilatation of the right auricle and right ventricle, but the pulmonary vessels were not even mentioned.

In cases in which cyanosis was a prominent clinical finding and in which atherosclerosis of the pulmonary artery was noted at necropsy the condition came to be labeled Ayerza's disease. Various views were expressed as to etiology, and when Warthin, in 1917, reported that he had found spirochetes in sections of an aneurysm of the pulmonary artery of a patient, who incidentally was not even cyanosed, he started an unwarranted wave of enthusiasm for accepting syphilis as at least one of the etiologic factors in Ayerza's disease. Meanwhile this name was used universally to denote a variety of anatomic lesions in the pul-

From the Mayo Foundation and the Division of Medicine, the Mayo Clinic

1 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation, Arch Int Med 56 976-1014 (Nov.) 1935

monary vessels and lungs, including probably primary or arteriolar pulmonary sclerosis. While the name inadvertently helped to attract attention to diseases of the pulmonary artery, it also helped to add to the confusion which exists concerning the nature of these diseases.

Study of the literature bearing on disease of the pulmonary artery is especially difficult, because authors have exercised insufficient discrimination in considering changes in the pulmonary artery and its larger branches, on the one hand, and those of the arteriolar system, on the other hand. To add to the difficulties, no uniform terminology is employed in defining the term arteriole. Finally, there is no clear understanding of what constitutes the pathologic changes of aging and what is definitely disease. Therefore, while a great many facts are known about pathologic changes in the pulmonary circulation, it is to be expected that a considerable amount of rearrangement will occur before they will finally appear in their proper perspective.

PATHOLOGIC CONSIDERATIONS

In approaching this study we accept in a general way the following facts relative to the pathologic changes in the pulmonary arterial tree.

Atherosclerotic changes of the pulmonary artery and its main branches are a frequent accompaniment of conditions associated with increased pressure within the pulmonary circulation. Mitral stenosis is perhaps the condition which most frequently is responsible for atherosclerotic changes in the pulmonary artery and its main branches, but Parker and Weiss² recently have described arteriolar changes in five of ten cases of mitral stenosis. These changes consisted of hyperplastic arteriolar sclerosis and arteriolar necrosis. They were not noted in five cases of congenital cardiac septal defect, in twelve cases of congestive circulatory failure of syphilitic and hypertensive origin, in fifteen cases of emphysema, in one case of marked kyphosis and sclerosis of the larger pulmonary arteries, in twenty cases of thrombosis or embolism of the pulmonary arteries, in nineteen cases of chronic interstitial pneumonia or in three cases of pulmonary fibrosis of noncardiac origin. In this connection it is interesting to know that the exposure of rats to compressed air was reported to lead in time to lesions in the small arterioles of the lungs. The lesions consisted of a thickening and hyalinization of the walls and ultimate thrombosis of many of the arterioles.³

2 Parker, Frederic, Jr., and Weiss, Soma. The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, *Am J Path* **12** 573-598 (Sept.) 1936.

3 Smith, F. J. C., Bennett, G. A., Heim, J. W., Thomson, R. M., and Drinker, C. K. Morphological Changes in the Lungs of Rats Living Under Compressed Air Conditions, *J Exper Med* **56** 79-89 (July) 1932.

Sclerotic changes are almost constantly present in the different subdivisions of the pulmonary circulation. Bienner⁴ observed some degree of microscopic atherosclerosis in 97 per cent of one hundred unselected cases in which necropsy was performed. He noted that its severity increases somewhat with age and with conditions which are thought to be associated with increased pulmonary arterial pressure. These observations correspond closely with the observations related to the systemic circulation, and in the absence of demonstrable disease elsewhere they possibly represent nothing more than changes incident to age. At any rate, they become important only when circulatory embarrassment results from their presence, and in this regard the vascular system seems to possess a reserve which is not readily exhausted.

Localized atherosclerotic or endarteritic changes frequently are associated with such lesions of the lung as abscesses, tuberculosis and bronchiectasis, and arteritis due to syphilis and that due to rheumatic fever are well recognized entities.

Diffuse sclerosis of the pulmonary arterioles may occur without obvious reason. Extensive sclerosis of the pulmonary arteries, such as that associated with cardiac or pulmonary disease, which occurs without any obvious reason, is a rare but well established pathologic entity. In this so-called primary pulmonary vascular sclerosis the important pathologic changes occur in the smaller arteries, and there is associated hypertrophy of the right ventricle. It is this type that is of special interest.

MATERIAL AND METHODS OF STUDY

Our approach to the problem of sclerosis in the pulmonary circulation is based on (1) the study of a group of cases in which there were sclerotic changes in the pulmonary arterial tree, (2) the clinicopathologic analysis of twelve of the cases in which there was diffuse sclerosis of the pulmonary arterioles and (3) the consideration of the physiologic principles on which these symptoms and changes may be based.

We selected twenty-nine cases in which detailed microscopic studies were carried out on all the divisions of the pulmonary artery. These cases may be divided into two groups: (1) sixteen cases in which there was gross evidence of sclerosis of the pulmonary artery, but no unusual microscopic evidence of arteriolar sclerosis, and (2) thirteen cases in which there was microscopic evidence of arteriolar sclerosis distributed diffusely throughout both lungs. In three of the first group of cases there was hypertrophy of the right ventricle. In two of these cases there was definite evidence of chronic mitral endocarditis, which in all probability accounted for the ventricular hypertrophy, but in the third case no adequate reason for the hypertrophy of the right ventricle could be found. This group requires no further comment, as the pathologic observations were similar to and corresponded

⁴ Brenner, O. Pathology of the Vessels of the Pulmonary Circulation, *Arch Int Med* 56:457-497 (Sept.) 1935.

with the accepted conceptions of atherosclerosis of the larger arteries in the systemic circulation. In eleven of the thirteen cases in which there was microscopic evidence of arteriolar sclerosis there was definite hypertrophy of the right ventricle.

Anatomic Criteria—One of us (D H K) has been able to determine in a series of sections of normal lungs of infants that muscle is present in the media of vessels with an outside diameter of 30 microns. With increasing age the muscular layer of the media is seen to be present only in vessels of progressively greater diameter. Thus, in cases in which the patients are from 70 to 80 years of age there is no muscle in the media of vessels with an outside diameter of less than from 160 to 180 microns. Hence, we have included as arterioles those vessels with an outside diameter of less than 300 microns, in order to make sure that we were well beyond the size of vessel in which pathologic changes and changes attributable to advancing age might be confused. This feature also obviated the necessity of adjusting our criteria of normalcy for each separate age group.

Grading of Sclerosis—After a careful consideration of the data in the cases in the second group, it was found that the sclerosis could be roughly grouped into four grades according to the degree of involvement. In sclerosis of grade 1 the initial arteriolar change appeared to consist of a thickening of the media (fig 1 A). This apparently was due to two elements, namely, an increase in elastic connective tissue and hypertrophy of the muscle fibers. This media thickening was associated with a splitting of the internal elastic lamina and an increase in elastic fibrils, some of these fibrils extended into the intima and the media from the elastic lamina. In sclerosis of grade 2 (fig 1 B), which followed or in some cases accompanied sclerosis of grade 1, there were patches of medial degeneration, which consisted of vacuolation, pyknotic nuclear changes, hyalinization and fatty changes. As the sclerosis progressed to grade 3 (fig 2 A) the intima became increasingly thickened by the formation of fibrous tissue, and the media in a comparable manner became gradually thinner. Thrombi were present in one case. These appeared to be of various ages, as some had undergone partial or complete organization. In sclerosis of grade 4 (fig 2 B), that is, the most advanced lesion noted in this group, the intimal thickening was intense and produced almost complete occlusion. In three cases the sclerosis was of grade 1, in four cases, grade 2, in four cases, grade 3, and in two cases, grade 4.

Associated Hypertrophy of the Right Ventricle—Finally an attempt was made to correlate the degree of sclerosis and the amount of hypertrophy of the right ventricle. As no practical method is known whereby the degree of hypertrophy of independent ventricles can be accurately computed, a rough estimation of the size of the ventricles was made, and the results were compared with what we consider to be the normal size of the right ventricle. This was carried out independently, without reference to the degree of vascular disease present in each case, in order to arrive at unbiased conclusions. The correlation showed a rather close ratio between the degree of arteriolar sclerosis and the degree of ventricular hypertrophy.

CLINICOPATHOLOGIC CONSIDERATION

Clinical data were available in twelve cases in which arteriolar changes were present. The twelve cases were further studied in order to determine whether any special features would be revealed by the recorded symptoms and objective changes which would be characteristic or suggestive of these arteriolar changes. The first noteworthy feature



Fig 1—A, arteriolar sclerosis, grade 1, $\times 510$ B, arteriolar sclerosis, grade 2, $\times 480$

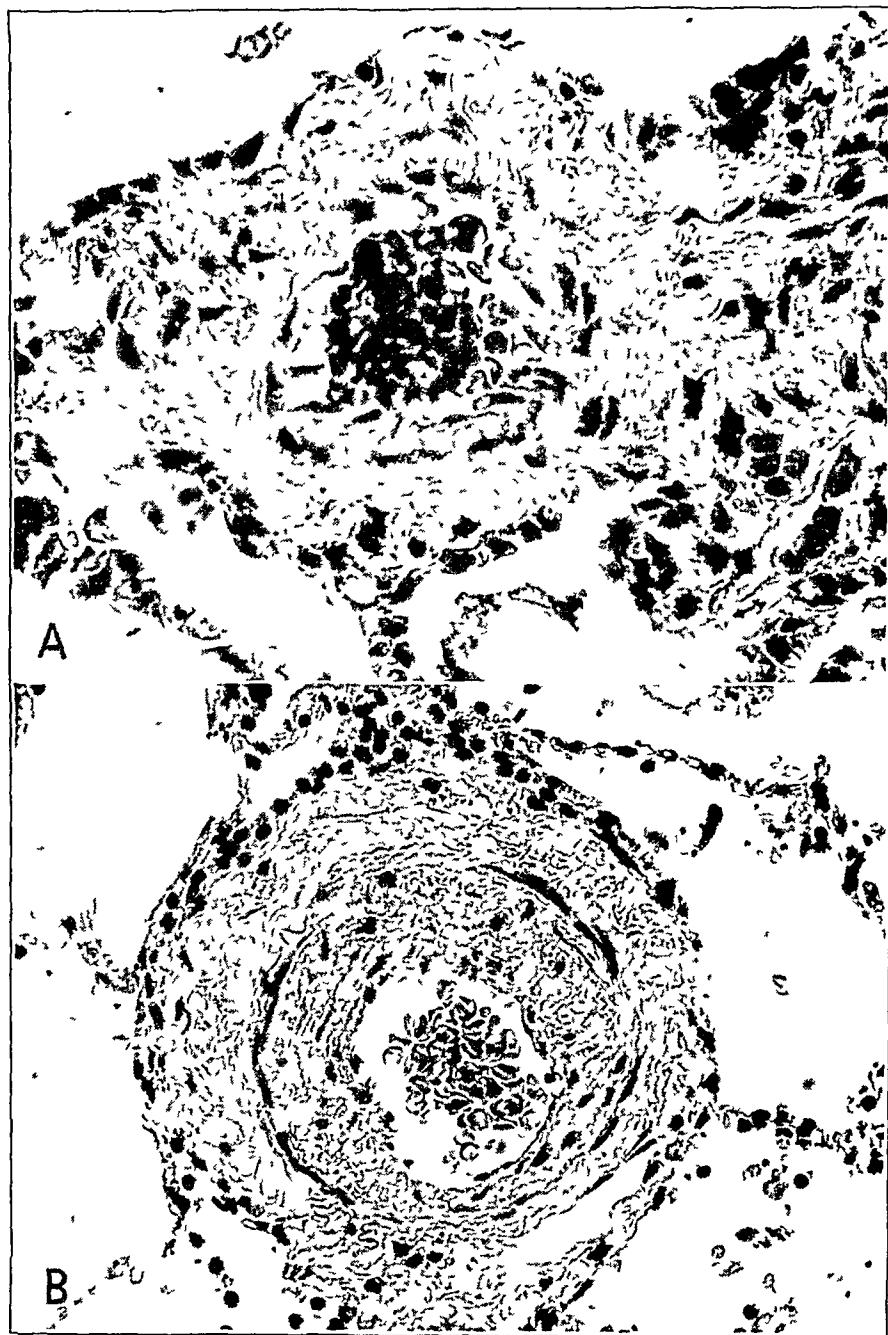


Fig 2—*A*, arteriolar sclerosis, grade 3, $\times 530$ *B*, arteriolar sclerosis, grade 4, $\times 385$

was the entire lack of correlation between the degree of arteriolar sclerosis and the degree of physiologic disturbance, in fact, on further analysis it immediately became apparent that these cases automatically divided themselves into the three following groups

Group 1 (Table 1) —This group consisted of four cases in which the cardiorespiratory symptoms were either in complete abeyance or appeared only as a terminal event. Yet in three of the cases in this group there was a rather marked degree of arteriolar sclerosis (table 1). Death seemed to be due to an unrelated disease.

CASE 1—A man aged 74 presented himself for examination because of abdominal symptoms, which proved to be due to carcinoma of the rectum. His only comment referable to the cardiorespiratory system was that his "wind was

TABLE 1—*Data on Cases of Arteriolar Sclerosis in Which There Were no Previous Cardiorespiratory Symptoms (Group 1)*

Case	Age, Years	Sex	Arteriolar Sclerosis, Grade	Hypertrophy of Right Ventricle, Grade	Cause of Death	Electrocardiographic Findings	Blood Pressure, Mm of Hg		Hemoglobin, Gm per 100 Cc of Blood	Erythrocytes, Millions per Cu Mm of Blood
							Systolic	Diastolic		
1	74	M	1	0	Carcinoma of rectum	Preponderance of left ventricle, iso electric T wave in lead I	210	100	13.0	3.89
2	44	M	3	3	Coronary thrombosis		120	70	14.8	4.87
3	68	M	3	1	Gastro intestinal hemorrhage	Preponderance of left ventricle, inversion of T wave in lead III	154	80	8.2	2.77
4	56	M	4	3	Postoperative pulmonary embolism		118	90	14.2	4.57

poor when the gas pressed up against the lungs." The value for the blood pressure, expressed in millimeters of mercury, was 210 systolic and 100 diastolic. The electrocardiogram showed left axis deviation, with an iso-electric T wave in lead I. The value for hemoglobin was 13 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 3,890,000 per cubic millimeter of blood. The patient died as the result of infection following resection of the rectum.

Summary—There was slight generalized pulmonary arteriolar sclerosis (grade 1), without symptoms.

CASE 2—A man 44 years of age had had symptoms of thrombo-angitis obliterans for nine years. There had been no symptoms referable to the cardiorespiratory system, and physical examination did not reveal any abnormality. The value for the blood pressure, expressed in millimeters of mercury, was 120 systolic and 70 diastolic. The value for hemoglobin was 14.8 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 4,870,000 per cubic millimeter of blood. Roentgenologic examination of the thorax did not disclose any abnormality. After cervical sympathectomy had been performed labored breathing and slight cyanosis developed, but these symptoms disappeared entirely after the patient had

been in an oxygen chamber for twenty-four hours. Eight months later lumbar sympathectomy was performed. Within a few hours, after a few gasping breaths, the patient died suddenly of coronary thrombosis.

Summary—There was arteriolar sclerosis of grade 3, without any symptoms except those which followed operation. There was nothing about the arteriolar sclerosis to suggest that it was related to thrombo-angitis obliterans.

CASE 3—A man aged 68 sought medical advice because of a general decline in health and because he had had a gastro-intestinal hemorrhage. There were no cardiac symptoms. Examination of the heart and lungs and roentgenologic examination of the thorax did not reveal any abnormality. The value for the systolic blood pressure was 154 mm of mercury and that for the diastolic pressure was 80 mm. The value for hemoglobin was 82 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 2,770,000 per cubic millimeter of blood. The electrocardiogram showed left axis deviation and an inverted T wave in lead III. The patient died after a massive hemorrhage, which proved to have been caused by an ulcerating carcinoma of the papilla of Santorini that had eroded into the duodenum.

Summary—There was marked pulmonary arteriolar sclerosis (grade 3), without symptoms.

CASE 4—A man aged 56 came to the clinic because of an indefinite ulcer-like type of indigestion which was relieved by the ingestion of food or alkali. He admitted that he had slight dyspnea on exertion. Roentgenologic examination of the thorax revealed only a tortuous aorta. The value for the systolic blood pressure was 118 mm of mercury and that for the diastolic pressure was 90 mm. The value for hemoglobin was 14.2 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 4,570,000 per cubic millimeter of blood. Roentgenoscopic examination of the stomach revealed a lesion in the prepyloric region. Exploration was carried out, and the postoperative course was uneventful until the tenth day, when the patient died suddenly of pulmonary embolism.

Summary—There was arteriolar sclerosis (grade 4) in the lesser circulation, with only slight symptoms. Death was due to postoperative pulmonary embolism.

Group 2—This group was represented by one case in which pulmonary arteriolar sclerosis was associated with a large substernal goiter, which displaced the trachea.

CASE 5—A man aged 66 came to the clinic because of cough, which had been present for many years but which had become worse in the previous two months and had been associated with increasing dyspnea on exertion. He had known of the presence of the goiter for twenty years. The goiter extended substernally and displaced the trachea. The basal metabolic rate was +33 per cent. The value for the systolic blood pressure was 170 mm of mercury and that for the diastolic pressure was 108 mm. The value for hemoglobin was 17.2 Gm per hundred cubic centimeters of blood. Examination of the heart and lungs did not reveal any abnormality. When thyroidectomy was attempted, so much respiratory difficulty developed that the operation was stopped, and the patient was temporarily transferred to an oxygen tent. No further surgical treatment was undertaken until two months later. Meanwhile the dyspnea had improved somewhat, but it was noted that the auricles fibrillated paroxysmally. At the time of thyroidectomy the surgeon noted that the right lobe of the thyroid gland was eight times the normal size and that the left lobe was twelve times the normal size, the trachea was con-

siderably distorted Although the patient was placed in an oxygen tent post-operatively, he had numerous spells of dyspnea and finally died Despite the occurrence of auricular fibrillation, there never was any evidence of failure

Summary—There was a combination of arteriolar sclerosis (grade 1) and interference with ventilation due to mechanical obstruction of the trachea

Group 3—This group was comprised of seven cases in which there were varying degrees of arteriolar sclerosis (table 2) Despite the difference in the degree of arteriolar involvement in these cases, the clinical picture and final outcome were strikingly uniform

TABLE 2—Data on Cases in Which Arteriolar Sclerosis was Associated with the Clinical Picture of Marked Congestive Heart Failure (Group 3)

Case	Age, Years	Sex	Arteriolar Sclerosis, Grade	Hypertrophy of Right Ventricle, Grade	Electrocardiographic Findings	Blood Pressure, Mm of Hg		Hemoglobin, Gm per 100 Cc of Blood	Erythrocytes, Millions per Cu Mm of Blood	Associated Pathologic Changes
						Systolic	Diastolic			
6	47	M	1	1	Preponderance of right ventricle, inversion of T wave in leads II and III	135	98	14.3	4.54	Coronary sclerosis, grade 3, healed myocardial infarction
7	57	M	1	3		120	82	18.0	4.06	Emphysema
8	45	M	2	3	Preponderance of right ventricle, exaggeration of P ₂ wave and inversion of T wave in leads II and III	136	108	17.0	4.78	Calcareous aortic stenosis
9	51	M	2	1		116	84			Asthmatic bronchitis
10	39	F	3	3	Preponderance of right ventricle, diphasic T wave in lead II and inverted T wave in lead III	94	68	13.5	3.95	Mitral stenosis
11	67	F	3	1		160	100	13.1	5.04	Emphysema and hypertension
12	51	M	4	3	Preponderance of right ventricle	120	80	16.3	5.68	Emphysema

CASE 6—For eight years a man aged 47 had experienced "gas pains," which had been associated with effort and had been relieved by rest The abdominal pain at times had been associated with pain in the left arm In the two years before he came to the clinic he noted dyspnea on exertion, but he no longer experienced the pain which previously had been present For three months before he came to the clinic the dyspnea increased to orthopnea There was edema of the legs, which was of recent origin Examination disclosed considerable congestion at the bases of the lungs, the liver extended several inches below the costal margin and there was peripheral edema Cyanosis was rather marked and became progressively worse The value for the systolic blood pressure was 135 mm of mercury and that for the diastolic pressure was 98 mm Roentgenologic examination of the thorax revealed cardiac enlargement A gallop rhythm was present There was a systolic bruit at the apex, and the pulmonic second sound was accentuated The value for hemoglobin was 14.3 Gm per hundred cubic centimeters of blood, and

the erythrocytes numbered 4,540,000 per cubic millimeter of blood. The electrocardiogram showed right axis deviation, with inversion of the T wave in leads II and III. There was considerable evidence of generalized arteriosclerosis. The patient did not respond to treatment. The clinical impression was that the symptoms were attributable to coronary disease, and it was suggested that he had had an occlusion of the posterior basal portion of the left ventricle or that he had disease of the pulmonary artery. Necropsy disclosed marked coronary sclerosis, a healed infarction and arteriolar sclerosis of the pulmonary vessels.

Summary—There was arteriolar sclerosis (grade 1) associated with advanced coronary sclerosis.

CASE 7—A man, aged 57 had enjoyed good health until two years before he came to the clinic, when he began to note discomfort in the upper part of the abdomen. About the same time he noted dyspnea on exertion. His condition remained about the same until a few months before he came to the clinic, when edema of the ankles, increasing dyspnea and cough became the predominant features. Examination revealed emphysema, orthopnea, distention of the veins of the neck, cyanosis, massive edema, and a systolic bruit, which was audible over the entire precordium. The value for the systolic blood pressure was 120 mm of mercury and that for the diastolic pressure was 82 mm. The value for hemoglobin was 17 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 4,060,000 per cubic millimeter of blood. Despite treatment, the patient became irrational, failed rapidly and died.

Summary—There was a combination of emphysema and arteriolar sclerosis (grade 1) of the pulmonary vessels.

CASE 8—A man aged 45 was first seen at the clinic in 1929. Dyspnea, cough and pain in the upper part of the abdomen developed two months before he came to the clinic, and he recently had had "influenza." The limbs were edematous, dyspnea was marked and there was some cyanosis. The liver was palpated 1½ inches (37 cm) below the costal margin. There was a systolic bruit, which was best heard over the aortic area, this was accompanied with a thrill. A definite diagnosis of aortic stenosis was made. It was noted that, despite an aortic lesion, the pulmonic second sound was accentuated, and the electrocardiogram showed right axis deviation, a diphasic T wave in lead II and an inverted T wave in lead III. Roentgenologic examination of the thorax revealed passive congestion at the bases of the lungs. The value for the systolic blood pressure was 136 mm of mercury and that for the diastolic pressure was 108 mm. The value for hemoglobin was 17 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 4,780,000 per cubic millimeter of blood. The patient responded satisfactorily to the administration of diuretics, he was allowed to return to his home but was advised to take maintenance doses of digitalis. He remained comfortable and free from edema for twelve months, he then caught cold, and the dyspnea and edema returned within a few weeks. His condition rapidly became worse, there were all the evidences of marked congestive heart failure. Despite the administration of diuretics he failed rapidly. Necropsy revealed calcareous aortic stenosis.

Summary—There was aortic stenosis (calcareous) associated with pulmonary arteriolar sclerosis (grade 2).

CASE 9—A man 51 years of age had had bronchial asthma for twenty years. He had been able to continue work, first as an iceman and later as a milkman, until five months before he came to the clinic, when he began to have severe attacks of dyspnea. The report does not state whether these differed in any

way from the former attacks of asthma. Two weeks before he came to the clinic the dyspnea became constant and severe, and there was rapidly developing edema. During this time he had considerable pain across the upper part of the abdomen. He was orthopneic and markedly cyanosed, the legs were edematous and there were moist râles at the bases of both lungs. The cardiac sounds were indistinct. The value for the systolic blood pressure was 116 mm of mercury and that for the diastolic pressure was 84 mm. The liver was palpable. The patient died a few hours after he was admitted to the hospital.

Summary—There were long-standing asthmatic bronchitis and sclerosis of the pulmonary arterioles (grade 2).

CASE 10—A woman aged 39 had had slight dyspnea on exertion for several years. Two years before she came to the clinic she had an illness which was described as influenza and bronchitis, afterward the dyspnea became progressively worse, and enlargement of the abdomen was noted. Finally edema of the legs developed. Repeated abdominal paracentesis was necessary. In the eight months before she came to the clinic she had a persistent cough and some fever. She presented a clinical picture of marked congestive heart failure with cyanosis, the veins of the neck were distended, and there was auscultatory evidence of mitral stenosis, including marked accentuation of the pulmonic second sound. Roentgenologic examination revealed fluid at the base of the right lung. The electrocardiogram showed right axis deviation, a diphasic T wave in lead II and an inverted T wave in lead III. The patient did not respond to treatment and failed rapidly. The predominance of ascites suggested the possibility of adhesive pericarditis, or at least it was felt that some condition was present in addition to mitral stenosis. The value for hemoglobin was 13.5 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 3,950,000 per cubic millimeter of blood. The value for the systolic blood pressure was 94 mm of mercury and that for the diastolic pressure was 68 mm.

Summary—There was mitral stenosis associated with marked pulmonary arteriolar sclerosis (grade 3).

CASE 11—A woman aged 67 had had asthmatic attacks for eighteen years, these had occurred mostly during the summer and had been associated with a chronic nonproductive cough. For five years she had become dyspneic after exertion. Edema of the ankles was first noticed two years prior to her visit to the clinic. After that the dyspnea which occurred after exertion became markedly worse, and there was evidence of increasing congestive heart failure. The value for the systolic blood pressure was 160 mm of mercury and that for the diastolic was 100 mm. There was a systolic bruit at the apex, otherwise the cardiac findings were not remarkable. The value for hemoglobin was 13.1 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 5,040,000 per cubic millimeter of blood. The clinical diagnosis was bronchial asthma, associated emphysema and hypertensive and arteriosclerotic heart disease with decompensation. It was suggested that the cardiac findings did not explain the clinical picture entirely.

Summary—There was a combination of emphysema, hypertensive and arteriosclerotic heart disease and pulmonary arteriolar sclerosis (grade 3).

CASE 12—The patient was a man aged 51 who had been a coal miner for thirty years. Nine years before he came to the clinic he began to suffer from dyspnea on exertion. This became so severe that he was obliged to stop work four years later. At that time he had attacks of choking at night, the choking was

relieved when he slept on his abdomen. At the same time pain developed in the upper part of the abdomen, it extended to the back and was associated with much nausea and vomiting. Two months later a cholecystectomy was performed because of the pain, but no details are available as to what was observed at that time. Two years before the patient came to the clinic he had a pulmonary hemorrhage. Eighteen months later he first noted edema of the ankles, at the same time an increase in the severity of the dyspnea and a recurrence of the abdominal pain were noted. His condition had become progressively worse. When he came to the clinic there was evidence of marked congestive heart failure. Examination disclosed massive edema, ascites, râles at the bases of the lungs, congestion of the liver and clubbing of the fingers. A systolic bruit was audible at the apex, and the pulmonic second sound was accentuated. The electrocardiogram revealed right axis deviation. These findings led the clinician to make a diagnosis of disease of the mitral valve. The interference with pulmonary ventilation was so great, however, that it was considered to be the result of emphysema rather than the result of the valvular heart disease. The value for the systolic blood pressure was 120 mm of mercury and that for the diastolic pressure was 80 mm. The value for hemoglobin was 16.3 Gm per hundred cubic centimeters of blood, and the erythrocytes numbered 5,680,000 per cubic millimeter of blood. The patient failed rapidly, in spite of the usual methods of treatment.

Summary—The presence of emphysema was confirmed at necropsy, and there was arteriolar sclerosis (grade 4) of the pulmonary arterioles.

Comment on Cases in Group 3—The typical picture seen in this third group of cases may be described as follows. In all the cases there was a history of dyspnea on exertion; the dyspnea had been present for several years and often had been initiated or, at any rate, aggravated by an intercurrent infection of the upper part of the respiratory tract. In two cases seasonal asthmatic attacks had occurred for several years. In some cases dyspnea was the only symptom for a time, but it was usually progressive, in some cases it was rapidly so. Distress in the upper part of the abdomen frequently was present and unquestionably was evidence of early congestive heart failure. Once objective evidence of congestive heart failure became manifest, the course proceeded rather rapidly down-hill, coughing became a troublesome symptom, edema became massive and dyspnea became extreme. Cyanosis should occur relatively early, but in this group of cases the patients were not seen at this stage of illness. In the final stages the signs of marked venous congestion and cyanosis were much in evidence, the patients became irrational and a semicomatose condition ushered in death. While in most respects this is the picture of failure of the right side of the heart, there are some rather interesting differences, namely, the rapid decline in the last phases and the almost entire lack of response to therapy which ordinarily affords at least temporary relief and often effects a diuretic diuresis, with resulting subjective improvement in cases of purely myocardial decompensation. Finally, the most important feature in these cases was the lack of correlation between the ascertainable cardiac changes, on the one hand, and the degree of physiologic derangement,

on the other. It is unusual for cardiac disease to be fatal in its first break of compensation if any reasonable therapy is combined with rest in bed. In only one case was there a history of congestive heart failure in which the patient responded satisfactorily to treatment a year before coming to the clinic. In this case there was also calcareous aortic stenosis, which might well have been the cause of the decompensation at that time. After a "cold" a second break in compensation occurred and terminated in a manner similar to that in the other cases in this group.

Further analysis of this group discloses that in each case an additional factor was present. In practically every instance the attending clinician commented on the fact that the heart disease seemed insufficient to account for all the clinical manifestations present.

PHYSIOLOGIC PRINCIPLES ON WHICH THE SYMPTOMS AND SIGNS MAY BE BASED

The whole matter might be dismissed with the inference that the coexistence of more than one pathologic process is in itself an adequate explanation. While this, in the main, is true, the problem of evaluating the relative significance of each individual factor concerned is as important as the recognition of its presence.

In an attempt to evaluate the effects of disease in the cardiac and pulmonary systems, it is well to review the mechanisms which produce the resulting symptoms.

The Mechanism of Congestive Heart Failure—Congestive heart failure results from a set of circumstances which cause the heart as a pumping organ to fail to supply blood in adequate amounts to meet the demands imposed by the daily activities of the patient. In other words, the heart fails to transfer blood effectively from the venous to the arterial side, so that pressure within the venous system is increased and as a result of increased venous pressure the speed of the blood flow diminishes, stasis occurs and edema develops. Except in the earliest stages of heart failure, this increased venous pressure can be elicited clinically. It is conceivable that when the cardiac reserve begins to be diminished, the lungs play a compensatory role by opening up the capillary bed in an attempt to increase the ventilating function. There is a great deal of evidence to show that the pulmonary vascular bed can expand and contract as required⁵. In the later phases of congestive heart failure, with the development of edema, there is actually an interference with gaseous exchange. The cardinal symptoms of heart failure,

⁵ Wearn, J. T., Barr, J. S., and Geiman, W. J. The Behavior of the Arterioles and Capillaries of the Lung, *Proc. Soc. Exper. Biol. & Med.* **24** 114-115 (Nov.) 1926. Drinker, C. K., Churchill, E. D., and Ferry, R. M. The Volume of Blood in the Heart and Lungs, *Am. J. Physiol.* **77** 590-624 (Aug.) 1926.

dyspnea, cyanosis, cough and diminished vital capacity, are also the symptoms of pulmonary disease, but the mechanism of their production is entirely different in these diseases

The Mechanism of Pulmonary Failure—The main function of the pulmonary system is to oxygenate venous blood. As one speaks of "cardiac reserve" and its loss in heart disease, it is convenient to speak of "pulmonary reserve," with the implication that the lung is able to become accommodated to varying amounts of work and that when it becomes diseased, or when its function is otherwise interfered with, there will be a loss of pulmonary reserve until a stage is reached at which the lungs can supply oxygen to venous blood at only a much retarded speed. Even if the heart is circulating blood at a normal or at even an increased speed, there will still be a relative deficiency of oxygen and hence dyspnea, for the immediate cause of dyspnea, no matter how it is produced, is a lack of oxygen in the tissues. Any process which interferes with the flow of oxygen to the alveoli of the lungs will have exactly the same effect as it did in case 5.

The Cardiorespiratory System as a Functional Unit—The cardiorespiratory system may well be considered as a functional unit. It is evident that the cardiac pump and the ventilating lung are functionally inseparable. It is interesting to visualize the simple arrangement in the fish. The heart, which contains only venous blood, discharges its contents by a system of afferent vessels into and through the gills, where gaseous exchanges occur. A corresponding group of efferent vessels conducts the oxygenated blood to the systemic circulation. The human cardiorespiratory system, while it is a complicated mechanism anatomically, corresponds to the same simple plan functionally. Thus, the right side of the heart discharges the venous blood into the lungs. The arteriolar system is interposed between the heart and the alveolar system, the radicles of the pulmonary vein and the left side of the heart constitute the efferent system and distribute the oxygenated blood to the systemic circulation. It is important to consider the nature of these components and the manner in which their function is affected.

Afferent System The right side of the heart and the pulmonary vessels are seldom the seat of primary disease. Disease of the tricuspid valve, pulmonic stenosis and abnormal shunts of blood associated with congenital lesions may throw added strain on the right ventricle and adhesive pericarditis may interfere with its function. Any disease in the pulmonary system or in the left side of the heart which will increase venous pressure will inevitably cause strain of the right ventricle, and if it lasts long enough it will cause failure of the right ventricle.

Arteriolar System We are presenting further evidence that arteriolar sclerosis is a definite pathologic entity and that it can occur as an

independent lesion in varying degrees of severity. Even less is known about its cause and its incidence than is known about the corresponding lesion in the greater circulation. That the right side of the heart can become adapted to the resistance arising from the presence of arteriolar sclerosis is well illustrated by the four cases in which, despite marked arteriolar changes in three and associated hypertrophy in the right ventricle in all but one, there was no appreciable deficiency in pulmonary circulation. While it did not occur in our series, failure of the right side of the heart may occur as a result of pulmonary arteriolar sclerosis alone, and it corresponds to what has been termed primary pulmonary vascular sclerosis.

Alveolar System Changes in the bony thorax, mechanical pressure on the air passages, gross destruction of parts of the lungs and structural changes in the bronchi, such as occur in chronic bronchitis, prevent a sufficient supply of air from reaching the alveolar system. By far the most important cause of diminished gaseous exchange in the lungs, however, is emphysema, which, in fact, is frequently associated with the conditions that have just been mentioned. The manner in which emphysema breaks down pulmonary reserve is essentially by diminishing the ventilating surface of the lungs.

It is rather universally believed that emphysema interferes with the pulmonary circulation, in the sense that it obstructs the current of blood in its course through the lungs, and that the hypertrophy of the right ventricle associated with emphysema is evidence of this obstruction. That the velocity of the flow of blood through the lungs is not necessarily slowed in emphysema has definitely been shown by Weiss and Blumgart.⁶ In fact, they have stated reasons for the belief that it might even be accelerated in some cases, which indicates that increased activity of the right ventricle is a purposeful mechanism that will serve to maintain a high minute volume flow and thereby help to compensate for the insufficient ventilation. This they suggested as an explanation for the hypertrophy of the right ventricle that sometimes occurs in emphysema. In this connection it is noteworthy that Alexander⁷ observed that hypertrophy of the left ventricle was an almost constant accompaniment of the hypertrophy of the right ventricle that was associated with emphysema. This phenomenon is difficult to explain on any other basis than that the left ventricle also is operating under strain. We venture the suggestion that the cases of emphysema in which congestive heart failure

⁶ Weiss, Soma, and Blumgart, H. L. Studies on the Velocity of Blood Flow. VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, *J. Clin. Investigation* 4: 555-574 (Oct.) 1927.

⁷ Alexander, H. L. Emphysema, *Proc. Staff Meet., Mayo Clin.* 10: 377-384 (June 12) 1935.

has been reported may not have been sufficiently studied to exclude arteriolar changes or that there may have been other factors aiding the mechanism which was crippling the cardiorespiratory reserve. It is especially significant that in the group of cases of emphysema studied by Weiss and Blumgart there was no increase in venous pressure except when the condition was complicated by independent heart disease. Interpreting their results conservatively, therefore, it seems that if increased resistance is offered to the lesser circulation by emphysema, it is seldom sufficient to cause embarrassment of the right side of the heart.

Efferent System The left side of the heart, or the efferent system, which distributes oxygenated blood throughout the entire greater circulation, is frequently the seat of organic disease, such as disease of the mitral and aortic valves, coronary sclerosis and hypertension. When its reserve is decreased so that it can no longer effectively propel the column of blood it receives from the pulmonary circuit the latter system becomes embarrassed, and its function is markedly altered.

We wish to point out that the pulmonary system can become adapted to increased work, but always at the expense of its reserve. When factors are already present, such as ventilating difficulties, irrespective of the cause, and when vascular disease, such as arteriolar changes, is present, the point at which the reserve is exhausted is rapidly reached. The complete breakdown of the two systems is compatible, at the most, with a limited existence and extreme discomfort.

CLINICOPATHOLOGIC CONCEPTION OF PULMONARY ARTERIOLAR SCLEROSIS

We believe that one type of pulmonary arteriosclerosis is the counterpart of arteriolar sclerosis in the greater circulation and that no matter how it is produced it is associated with hypertension in the lesser circulation. The degree of sclerosis and the degree of hypertrophy of the right ventricle correspond as closely as do sclerosis of the systemic arterioles and hypertrophy of the left ventricle. In both instances one is dealing with systems endowed with considerable reserve, so that functional efficiency can be maintained for a long time in spite of extra strain.

This type of pulmonary arteriolar sclerosis is a diffuse process throughout the lungs, corresponding to diffuse sclerosis in the systemic circulation. It interferes mechanically with the flow of blood through the pulmonary circuit unless the pressure behind it is enough to overcome this peripheral resistance. This is only a compensatory mechanism and, like all compensatory mechanisms, will be adequate for a certain period—sometimes almost indefinitely. Moreover, like other compensatory mechanisms, it curtails that quality of variability in function which

characterizes normally functioning organs, that is, it is working at full capacity at all times. If the lesser circulation has only its own problems to contend with, it is remarkable how efficiently it can continue to function. The last straw from extraneous sources which will tip the scale against it need not be of appreciable dimensions. These facts are amply exemplified by even this small group of cases.

SUMMARY

The vascular diseases of the pulmonary arterial tree have many features in common with those of the general circulation. Some evidence of microscopic sclerosis is present in one or the other of the divisions of the pulmonary tree in practically all adults. It increases with age and especially in conditions associated with increased pressure in the lesser circulation. Atherosclerosis of the pulmonary artery and its larger branches seldom interferes appreciably with the mechanics of the circulation except, perhaps, so far as it occurs at the expense of the normal elasticity of the vessels. Sclerosis which involves the small muscular arteries (or arterioles) of the pulmonary circulation and its effects have not been sufficiently distinguished from similar changes in the larger branches of the pulmonary artery. A certain degree of microscopic arteriolar sclerosis must be regarded as a normal accompaniment of physiologic aging.

There is a separate entity, however, in which diffuse sclerosis of varying degree occurs throughout the arteriolar system of the entire lesser circulation and is comparable to a similar process in the systemic circulation. In the pulmonary circulation, too, the question as to whether these changes are primary or the result of other states of abnormal physiology is unsettled. It is usually associated, at any rate, with hypertrophy of the right ventricle. The entire vascular system seems to be endowed with a considerable reserve, for this type of arteriolar sclerosis does not necessarily cause circulatory embarrassment. When it does and when there is no apparent cause for it, such as cardiac or pulmonary disease, the term primary pulmonary vascular sclerosis has usually been applied to it. In our opinion this is merely an extreme degree of arteriolar sclerosis, and the atherosclerotic changes in the pulmonary artery itself when present are probably secondary to the pulmonary hypertension associated with the arteriolar sclerosis. Similar changes in the pulmonary artery and its main subdivisions have been known for years to occur in cases in which pulmonary hypertension was attributable to other causes, for example, mitral stenosis. We believe that it will clarify the problem considerably if the term pulmonary arteriolar sclerosis is substituted for the term primary pulmonary vascular sclerosis.

In all except three of the sixteen cases in which only the pulmonary artery and its main branches showed atherosclerotic changes, hyper-

trophy of the right ventricle was absent, in two of these three cases there was mitral stenosis, and in the third case there was no adequate explanation for the hypertrophy of the right ventricle.

We studied thirteen cases in which there were varying degrees of diffuse pulmonary arteriolar sclerosis. Hypertrophy of the right ventricle was present in eleven of these cases. In twelve cases clinical details were available, and their study revealed that in four cases (in three of which the sclerosis was marked) there were no cardiorespiratory symptoms, except as terminal phenomena. The patients died of unrelated causes. In one case there was a huge substernal goiter, and death followed its surgical removal. In this case there was no evidence of congestive heart failure. In the remaining seven cases the clinical picture, which was strikingly uniform in its evolution and final outcome, consisted essentially of dyspnea, which had been present for varying periods, and ended in a dramatic type of extreme congestive heart failure with cyanosis. There was an entire lack of response to treatment. In every instance an additional factor, either cardiac or pulmonary, was present, but at the same time it was not sufficiently advanced to be a satisfactory explanation for the presence of the extreme degree of physiologic derangement.

SEVERE ANEMIA OF APLASTIC TYPE ASSOCIATED WITH SCLEROSIS OF THYROID GLAND

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In a previous publication I¹ described a sclerosing disease of the thyroid gland which affects elderly women and is associated with marked hypochromic or hyperchromic anemia. Since the patients do not show signs of myxedema, the grave disturbance of the thyroid gland is likely to be overlooked unless a basal metabolism test is made. The lack of response to liver or iron medication then leads to the conclusion that one is dealing with an obscure primary anemia which cannot be classified. Study of the structure of the blood cells and of the hemoglobin metabolism does not help much in gaining any definite information as to the nature of the anemia, and in the terminal stage a blood picture may develop which is suggestive of aplastic anemia. The recent observation of an additional case that falls into this group induces me again to emphasize the importance of endocrine disturbances, particularly insufficiency of the thyroid gland, in the pathogenesis of obscure anemia.

REPORT OF A CASE

History—At the age of 50 years the patient, a married woman, attended an outpatient clinic because of obesity. At that time she weighed 231½ pounds (105 Kg), having gained 35 pounds (16 Kg) in two years. She complained also of occasional sharp headaches, nervousness, twitching of muscles, especially of the face, and slight loss of control of the urinary bladder. The record referred to myxedema, with a question mark. The blood pressure was 170 systolic and 90 diastolic, and the basal metabolic rate was minus 32.8 per cent. With thyroid medication and a proper diet the patient's condition improved markedly, her weight dropped to 201½ pounds (91 Kg) within three months and the record stated that she looked like a different woman.² Later she failed to visit the clinic, and no further information could be obtained concerning her condition.

Three years later, at the age of 53, she entered the Cook County Hospital, stating that she had been in fair health until three months before entry, when she contracted the "flu". She noticed general aching, fever and chills and had a slight nonproductive cough. Three weeks prior to entry she had rather severe diarrhea, which lasted for three days. She had been losing weight and experiencing a slight burning sensation on urination. She had also had several fainting spells. She had passed through the menopause at the age of 50 and had three children, all living and well.

† Dr Jaffé died on Dec 17, 1937.

From the Department of Pathology of the Cook County Hospital.

1 Jaffé, R H. Chronic Thyroiditis, J A M A **108** 105 (Jan 9) 1937.

2 The foregoing data were supplied by the St. Luke's Hospital.

Physical Examination—Physical examination revealed an obese woman who appeared acutely ill. The temperature was 103.2 F, the pulse rate 104, the respiratory rate 20 and the blood pressure 114 systolic and 68 diastolic. The skin was pale but elastic and moist, and there was no anomaly of the hair growth. The thyroid gland could not be palpated. The peripheral lymph nodes were not enlarged. Examination of the heart did not disclose any abnormal findings. There was slightly impaired resonance over the base of the lower lobe of the left lung, with moist râles in this region. On palpation there was slight tenderness in both lower quadrants of the abdomen. The spleen and liver could not be felt.

Laboratory Findings—The urine contained much albumin and many pus cells and degenerated epithelial cells. The urea nitrogen content of the blood was 16.8 mg per hundred cubic centimeters, and the icterus index was 5.35. The Kahn test was negative. Cultures of the blood remained sterile.

The hemoglobin content of the blood was 33 per cent (Sahl), and the erythrocyte count was 1,440,000. The color index was 1.1. There were 700 white blood cells, of which 79 per cent were lymphocytes, 14 per cent monocytes and 7 per cent neutrophilic leukocytes. Slight anisocytosis and poikilocytosis were noted, and 2 normoblasts were found per hundred white blood cells. The platelets were so small and scanty that they could not be counted.

Diagnosis—The differential diagnosis rested between aplastic anemia, aleukemic leukopenic leukemia and anemia due to thyroid deficiency. The patient's condition did not permit repeating the basal metabolism test.

Course—The patient received many blood transfusions, a proprietary preparation of fresh liver and a diet rich in liver. After each transfusion she showed some improvement, with slight signs of regeneration of the blood. The red cell count temporarily increased to 2,410,000 and the white cell count to 1,550. In the second week of her stay in the hospital aspiration of sternal bone marrow was made, and study showed a total cellularity of about 105,000 nucleated cells per cubic millimeter. The differential count showed myeloblasts, 0.4 per cent, neutrophilic myelocytes, 10.8 per cent, staff nucleated neutrophils, 2.4 per cent, mature neutrophils, 1.2 per cent, eosinophilic myelocytes, 0.4 per cent, erythrogonia (proerythroblasts), 5.2 per cent, erythroblasts, 21.2 per cent, normoblasts, 35.2 per cent, lymphocytes, 3.6 per cent, monocytes, 4 per cent, megakaryocytes, 0.4 per cent, and large deeply basophilic cells, 15.2 per cent. The deeply basophilic cells resembled erythrogonia. The structure of the nucleus may be described as halfway between that of a hemocytoblast and that of an erythrogonium. The cytoplasm of these cells as well as that of many other young cell forms revealed striking vacuolation (fig 1). The erythroblasts and normoblasts, however, were not affected by the vacuolation. The neutrophilic leukocytes were small, with poorly defined granulation and abnormally lobulated nuclei. The result of biopsy of the bone marrow may be summarized as showing diminished activity, with marked depression especially of granulopoiesis. The erythropoiesis went back to very young forms, which revealed evidences of toxic alteration (vacuolation). The diagnosis still remained doubtful.

The patient received daily injections of liver extract, which did not seem to have much effect. The temperature remained high and septic. She became irrational and died three weeks after admission to the hospital.

Gross Necropsy Observations—At the time of death the patient weighed 79 Kg. The body length was 175 cm. There were no signs of myxedema. Marked generalized anemia and focal bronchopneumonia were noted in the upper and lower lobes of the left lung. In the region of the trigon of the urinary bladder the

deeply injected mucosa was covered by adherent granular membranes that were light grayish brown. The heart weighed 335 Gm, and the myocardium was pale and friable. The weight of the spleen was 285 Gm, that of the liver, 1,910 Gm, and that of the kidneys, 345 Gm. The pancreas weighed 85 Gm, the adrenal glands, 16 Gm and the brain, 1,160 Gm. The hypophysis measured 15 by 10 by 6 mm. The bone marrow of the femur was soft and light purple-red.

Dissection of the soft parts of the neck revealed no definite thyroid gland. In place of the gland there was a soft thin and flat plate which measured 4 mm in thickness, weighed 7 Gm and seemed to fuse with the surrounding fat tissue.

Microscopic Observations—The plate which was present in place of the thyroid gland was composed of dense fibrillar connective tissue which enclosed islands

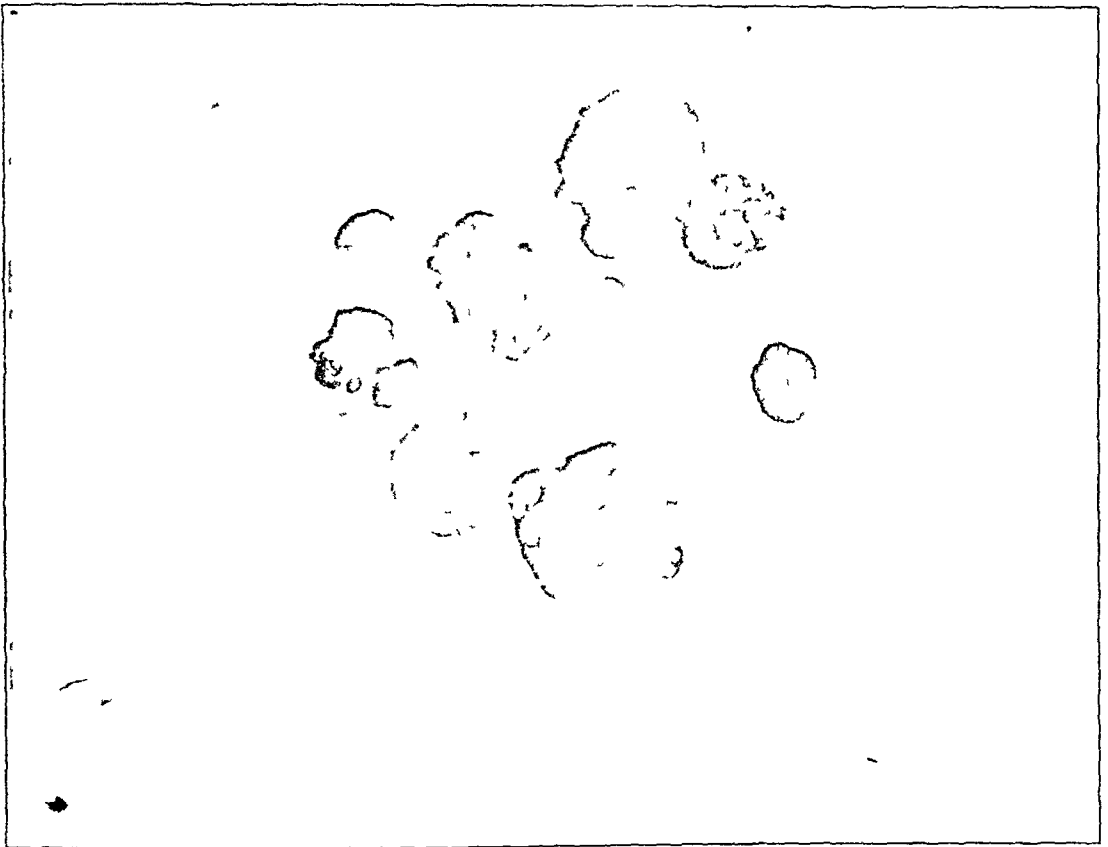


Fig 1—Smear of aspirated sternal bone marrow stained according to the Wright method, $\times 1,200$. Note the two very young erythropoietic cells and the monocyte with vacuolation of the cytoplasm. A large, basophilic erythroblast and two normoblasts are free from vacuoles.

of fat tissue. This connective tissue passed without a definite border into the surrounding fat tissue. Here and there a circumscribed accumulation of small lymphocytes with a few plasma cells was noted, arranged about small groups of cuboidal and polygonal cells with an ample, finely granular and pinkish stained cytoplasm and oval, deeply stained and relatively small nuclei which were often crenated (fig 2). With sudan III stain the cytoplasm of these cells became light brown. An occasional group of cells enclosed a small drop of pale colloid. Because of the extreme shrinking of the gland the arteries came to lie close together (fig 3). The walls of these arteries were moderately thickened and often infiltrated by fine lipid granules.

The bone marrow of the femur was 17 per cent cellular. There were many extravasations of blood, and the red cells varied in size and staining qualities. Some of them were rich in hemoglobin, others were brownish and gave a diffuse reaction to stain for iron. The reticulum cells were swollen and often contained red blood cells and normoblasts. The bone marrow cells formed small isolated and fairly compact islands of the following composition: neutrophilic myelocytes, 78 per cent, eosinophilic myelocytes, 08 per cent, erythrogonia, 18 per cent,



Fig 2—Section of the thyroid gland, showing accumulation of lymphocytes about a distintegrating follicle, $\times 150$

erythroblasts, 12.6 per cent, normoblasts, 72.8 per cent, plasma cells, 3.8 per cent, and megakaryocytes, 0.6 per cent.

Of the other microscopic observations, mention should be made of the marked fatty infiltration and moderate hemosiderosis of the hepatic cells, the slight fatty degeneration of the myocardium and of the renal epithelium, the marked congestion and hemosiderosis and slight myeloid metaplasia of the spleen, the atrophy

of the ovaries, with many albuginous corpora and iron deposits around them, and the decreased lipid content of the adrenal cortex. The parathyroid glands and the pancreas were not unusual. In the anterior lobe of the hypothesis the basophilic cells which predominated were often vacuolated. The intermediary portion contained medium-sized colloid-filled follicles, and single cords of cells of the intermediary portion were seen extending for a short distance into the loose posterior lobe.

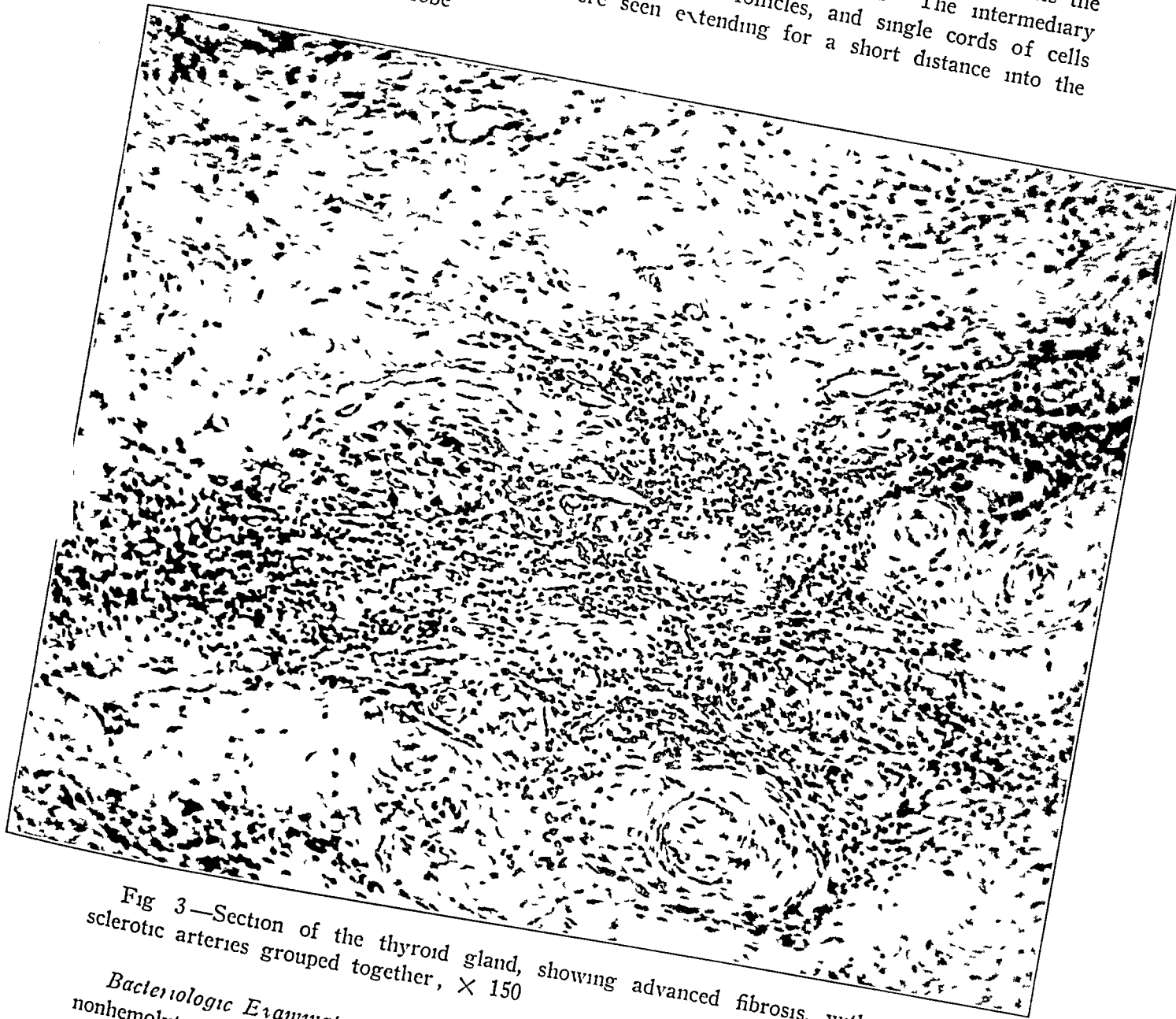


Fig 3—Section of the thyroid gland, showing advanced fibrosis, with the sclerotic arteries grouped together, $\times 150$

Bacteriologic Examination—Culture of material taken from the spleen showed nonhemolytic streptococci, Staphylococcus albus and Bacillus coli

Anatomic Diagnosis—The diagnosis was advanced fibrotic atrophy of the thyroid gland, severe generalized anemia, necrotizing cystitis, infectious hyperplasia and hemosiderosis of the spleen, fatty changes and hemosiderosis of the liver, slight fatty degeneration of the myocardium and of the liver, focal bronchopneumonia of the left lung and obesity

COMMENT

The question of anemia in myxedema has recently been well discussed by Holbøll,³ who stated that only in a few of the recent articles on myxedema has the condition of the blood been considered in detail (see also the article by Hatlehol⁴). He described the hematologic findings for twenty-eight patients with myxedema, all of whom were women from 35 to 64 years of age. In the majority of cases the basal metabolic rate was below minus 70 per cent. The anemia was of either hyperchromic or hypochromic type, with color indexes between 0.8 and 1.31, hemoglobin readings between 50 and 90 per cent and erythrocyte counts between 2,500,000 and 4,500,000. In one case myxedema was combined with true pernicious anemia. Holbøll emphasized that the anemia of myxedema does not respond well to any form of antianemic treatment save thyroid medication, and he said he considered this specific response as indicating that the anemia is due to thyroid deficiency.

The publications of Holbøll and of other investigators have shown that the anemia in myxedema is usually slight or of moderate degree, and it appears therefore that it is especially in the cases of thyroid deficiency without the signs of myxedema that the severe forms of anemia are encountered. Recently examination *in vivo* of the sternal bone marrow has been widely used, the main value of this method lying in the differentiation of true aplasia of the bone marrow from pseudo-aplasia (disturbance of maturation) and in the recognition of atypical leukemias.

When I received the specimen of bone marrow from the patient with thyroid sclerosis, a week and a half prior to her death, she was in a septic state. Judging from the cell content of the aspirated bone marrow, the functional activity of the marrow was depressed, and this depression was evident also from the postmortem examination of the femoral bone marrow. There were no signs of so-called maturation arrest, a term which I feel is often misused in modern hematologic literature. All stages of maturation and differentiation were found side by side, and the erythropoiesis showed very immature forms, which may be designated as intermediary between the hemocytoblast and the erythronium stage. These young cells showed signs of toxic alteration, in the form of vacuolation of the cytoplasm, and at the time of death had disappeared from the marrow. The condition of the bone marrow therefore can be described as of diminished activity.

The question may be raised whether the terminal septic condition, which could be traced to necrotizing cystitis, could account for the blood picture of aplastic anemia. One of my patients with sclerosis of the

3 Holbøll, S. A. *Acta med Scandinav* **89** 526, 1936.

4 Hatlehol, R. *Norsk mag f lægevidensk* **92** 453, 1931.

thyroid gland and with a similar blood picture, previously reported on, died of lobar pneumonia. However, the changes in the urinary bladder were too insignificant to account for the severe alteration of the blood picture, and I believe that the depression of the blood formation predisposed to and preceded the cystitis, as necrotizing inflammation of the mucous membranes is likely to develop in aleukocytic conditions.

In this case, as in my previous cases of sclerosis of the thyroid gland, the other endocrine glands did not reveal any significant changes. The hypophysis was slightly enlarged, and the basophilic cells predominated in the anterior lobe and showed increased vacuolation. The reports in the literature on the behavior of the hypophysis in acquired thyroid deficiency in men have varied. Some authors have referred to marked enlargement of the anterior lobe, while others have not recorded any abnormality.

The microscopic observations permit the conclusion that the sclerosis of the thyroid gland developed from a diffuse lymphocytic infiltration of the gland, residues of which were still present in the form of lymphocytic aggregations about degenerating follicles. There were no indications of an infective nature of the process, and I am of the opinion that the condition was due to the excessive involution of the thyroid gland that takes place with advancing age, particularly in women.

SUMMARY

A case of severe anemia of aplastic type in an elderly obese woman is described which offered great diagnostic difficulties. At autopsy the thyroid gland was observed to have been completely replaced by dense scar tissue, and there were signs of depressed activity of the bone marrow. The patient did not show symptoms of myxedema. Three years prior to death the patient's basal metabolic rate was minus 32 per cent.

GONOCOCCIC ENDOCARDITIS

A STUDY OF TWELVE CASES, WITH TEN POSTMORTEM EXAMINATIONS

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According to the historical review by Newman,¹ the first report of gonococcic infection involving the heart was published by Ricord, in 1838, and the first investigator to recover gonococci from the blood stream was Rothmund, in 1889. Hewes,² in 1894, cultured gonococci from the blood of 2 patients with gonococcic arthritis. Thayer and Blumer,³ in 1895, recovered the organism from the blood of a patient with endocarditis.

Since the establishment of endocarditis as a definite complication of gonorrhea, over a hundred papers have appeared on this subject. Most of these have been reports of individual cases. Thayer,⁴ in 1922, reported 20 cases in which necropsy was performed at the Johns Hopkins Hospital and reviewed the reports of 60 cases previously described. More recently reviews have been published by Stone,⁵ Newman,¹ McCants,⁶ Kirkland,⁷ Hoffman and Taggart,⁸ and Solomon and his associates.⁹ Estimates of the number of acceptable reports of cases have varied a great deal with different authors, depending on the criteria used in the diagnosis. Karsner¹⁰ stated, and Hoffman and Taggart

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1 Newman, Albert B. The Prognosis in Gonococcal Endocarditis, *Am Heart J* **8** 821 (Aug) 1933

2 Hewes, H F. Two Cases of Gonorrheal Rheumatism with Specific Bacterial Organisms in the Blood, *Boston M & S J* **131** 515 (Nov) 1894

3 Thayer, W S, and Blumer, G. Ulcerative Endocarditis Due to the Gonococcus. Gonorrheal Septicemia, *Bull Johns Hopkins Hosp* **7** 57 (April) 1896

4 Thayer, W S. Cardiac Complications of Gonorrhea, *Bull Johns Hopkins Hosp* **33** 361 (Oct) 1922

5 Stone, Eric. Gonorrheal Endocarditis, *J Urol* **31** 869 (June) 1934

6 McCants, J M. Gonococcus Infection of the Heart, *U S Nav M Bull* **28** 603 (July) 1930

7 Kirkland, H B. Gonococcus Endocarditis. Report of a Case, *Am Heart J* **7** 360 (Feb) 1932

8 Hoffman, A M, and Taggart, F C. Gonococcic Endocarditis, *Ann Int Med* **5** 397 (May) 1932

9 Solomon, P, Hurwitz, D, Woodall, M, and Lamb, M. Diagnosis of Gonococcus Endocarditis, *Arch Int Med* **52** 1 (July) 1933

10 Karsner, Howard T. The Pathology of Endocarditis. Summary Review, *J A M A* **96** 411 (Feb 7) 1931

said they agreed, that "a case of gonococcal endocarditis must show the presence of gonococci in the blood or lesion to be accepted as such." Other authors have observed less rigid diagnostic criteria. Almost all have agreed, however, that less than 150 authenticated cases have been reported. The purpose of this communication is to record an analysis of and comments on 12 additional cases of gonococcic endocarditis, in 10 of which a postmortem study was made by my colleagues and myself.

CLINICAL FINDINGS

Incidence—During the last twelve years there were admitted to the wards of the Vanderbilt University Hospital 12 patients (table 1) with gonococcic endocarditis, 10 of whom were examined post mortem. During this period 1,719 autopsies were performed. In 38 instances either acute or subacute endocarditis was present, the gonococcus being responsible in 10 cases, *Streptococcus haemolyticus* in 8, *Streptococcus viridans* in 7, a staphylococcus in 4, a pneumococcus in 2, the influenza bacillus in 2, unidentified organisms in 2, a diphtheria bacillus in 1, a paratyphoid bacillus in 1 and an unidentified streptococcus in 1. Thus it is seen that the gonococcus was the etiologic agent in 26 per cent of the cases and occurred about once in every 200 autopsies made as a routine. Thayer has stated the opinion that gonococcic endocarditis is not rare, since in 11 per cent of 176 instances of bacterial endocarditis (acute and subacute) he found the gonococcus. A streptococcus was present in 57 per cent of the remainder, a pneumococcus in 14 per cent, *Staphylococcus aureus* in 13 per cent, the influenza bacillus in 4 per cent and *Staphylococcus albus* in 1 per cent. In about 4 per cent of a series of patients with acute bacterial endocarditis studied in Boston¹¹ gonococci were found. Cabot,¹² in an earlier study, said that he had failed to find an instance of gonococcic endocarditis in 1,906 necropsies on patients with heart disease, although 180 had some form of endocarditis.

Age—The ages of our patients ranged from 19 to 69 years. It is of interest to note that 4 patients were over 50 years old. The average age was 36 years. Fifty-three of the 85 patients with "proved" gonorrheal endocarditis whose cases were reviewed by Stone were between the ages of 15 and 35 years, although the extremes were 2 and 51 years.

Sex—There were 7 women and 5 men in our group. In Thayer's group 72 per cent were males, and in Stone's group 62 per cent ("proved" group) were males.

11 White, P. D. Heart Disease, ed 2, New York, The Macmillan Company, 1937, p. 254.

12 Cabot, Richard C. Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 570.

TABLE 1—Summary of Clinical and Pathologic Data

Case	Age, Sex	Race	Interval Since Primary Infection	Duration of Endocarditis	Chills	Cardiac Signs	Emboic Phenomena		Average Daily Maximum Temperature, F	Highest White Cell Count	Lowest Hemoglobin Value, Gm
							Petechiae	Others			
1	69 M	W	14 yr plus	7 wk	Few	Moderate enlargement, coarse systolic apical murmur widely transmitted, systolic thrill over apex	Many (some with central necrosis)	+	102.5	10,500	90
2	22 F	W	3 wk	2 wk	Many	Moderate enlargement, with classic signs of aortic insufficiency	Many	0	104.0	13,300	102
3	19 M	W	?	3 wk	Many	Loud, coarse systolic apical murmur, with short presystolic rumble, accentuated P ₂ wave	Few	0	103.0	29,100	70
4	33 F	W	?	13 wk	Many	Long, loud, rough systolic apical murmur and short presystolic rumble	Few	In femoral artery	105.0	20,000	48
5	69 F	W	?	5 wk	Many	Typical signs of aortic insufficiency	0	Cerebral?	103.5	14,200	140
6	18 F	W	2 mo	10 days	Many	Typical signs of aortic insufficiency	0	0	104.2	13,400	110
7	54 M	W	1 mo	5 wk	Many	Dull systolic apical murmur	0	+	?	53,700	40
8	30 M	W	7 mo	2 wk	Many	Typical signs of aortic insufficiency	0	0	104.4	23,000	70
9	57 M	N	?	8 wk	Many	Long, loud, rough systolic apical murmur, accentuated P ₂ wave, slight cardiac enlargement	0	In femoral artery	103.0	26,800	120
10	24 M	N	?	5 wk	Many	Long, loud, harsh systolic murmur over apex, transmitted to left axilla and over entire precordium, P ₂ wave accentuated	Few	+	105.3	19,100	80
11	45 F	W	3 wk?	12 days	Many	Wavy impulse over precordium, slight presystolic apical thrill, moderate enlargement of left side, moderately loud diastolic rumble over apex, loud blowing apical systolic murmur, well transmitted, classic signs of aortic insufficiency	Few	0	105.0	15,800	103
12	22 F	W	?	14 wk	Many	Wavy impulse over precordium, slight cardiac enlargement, blowing systolic apical murmur transmitted over precordium and to left axilla	Few	+	103.5	17,350	55

* Due to gonococci

† Main cause of death

Clinical Impression	Chief Anatomic Diagnoses	Bacteriologic Findings
Malignant endocarditis (mitral),* acute cardiac failure,† urethritis,* embolic glomerular nephritis, arthritis,* uremia	Autopsy not permitted	Gonococci obtained from urethra and knee, 3 sterile blood cultures
Malignant endocarditis (aortic),* acute cardiac failure,† endocervicitis,* multiple arthritis*	Acute endocarditis (aortic), with rupture of cusps, abscess of wall of left ventricle and acute focal myocardial necrosis,* infarcts of spleen, acute endometritis, acute focal interstitial pancreatitis	Gonococci obtained from cervix, endometrium, 2 blood cultures (ante mortem) and aortic valve
Malignant endocarditis (mitral),* multiple arthritis,* subsiding 6 wk preceding death, acute glomerulonephritis, uremia †	Acute endocarditis (mitral),* acute myocarditis,* acute glomerular nephritis, acute splenitis, bilateral pleuritis with effusion, abdominal ascites	Gonococci obtained from blood culture (ante mortem) and vegetation on cardiac valve (smear)
Malignant endocarditis (mitral),* endocervicitis,* embolic glomerular nephritis, femoral embolism, uremia,† jaundice	Same as clinical impression, plus acute splenitis and infarction of spleen	Gonococci obtained from cervix and 4 blood cultures (ante mortem)
Malignant endocarditis (aortic),* chronic pelvic inflammatory disease,* embolic glomerular nephritis, uremia, pneumonia, cerebral embolism †	Acute endocarditis (aortic),* chronic urethritis,* intracapillary glomerular nephritis	Gonococci obtained from cervix and by smear and culture of vegetation on cardiac valve, 4 sterile antemortem blood cultures
Malignant endocarditis (aortic),* acute cardiac failure,† endocervicitis,* tenosynovitis,* multiple arthritis,* subsiding 3 wk before death	Acute endocarditis (aortic and mitral),* acute focal myocarditis,* septic infarcts of spleen and kidneys, embolic glomerular nephritis, embolic pneumonia, acute splenic tumor	Gonococci obtained from cervix and blood culture (ante mortem)
Malignant endocarditis (mitral),* urethritis,* acute nephritis, uremia †	Acute endocarditis (mitral),* septic infarcts of myocardium, spleen, kidneys, acute intracapillary glomerular nephritis, acute urethritis, acute focal pancreatitis, acute splenitis	Gonococci obtained from blood culture (ante mortem) and from vegetation on cardiac valve (smear)
Malignant endocarditis (aortic),* acute cardiac failure,† chronic endocervicitis,* multiple arthritis,* tenosynovitis*	Acute endocarditis (aortic),* acute focal myocarditis, acute pelvic peritonitis, chronic endocervicitis,* subacute intracapillary glomerular nephritis, acute salpingitis, infarcts of spleen, acute splenitis, acute embolic pneumonia	Gonococci obtained from cervix and vegetation on cardiac valve (smear), 7 sterile blood cultures
Malignant endocarditis (mitral),* acute cardiac failure,† femoral embolism, chronic urethritis,* multiple arthritis,* subsiding 5 wk before death, jaundice	Acute endocarditis (mitral),* femoral thrombosis, acute focal glomerular nephritis, acute and chronic prostatitis, central necrosis of liver	Gonococci obtained from 2 blood cultures (ante mortem) and vegetation on cardiac valve (smear)
Malignant endocarditis (mitral? or tricuspid),* syphilitic cirrhosis of liver (?), embolic glomerular nephritis, uremia,† jaundice, ascites, multiple arthritis,* subsiding 9 wk before death	Acute endocarditis (mitral),* cirrhosis of liver, syphilitic infarcts in spleen, jaundice, ascites, embolic glomerular nephritis	Gonococci obtained from 3 blood cultures (ante mortem)
Malignant endocarditis (mitral and aortic),* rheumatic heart disease, with mitral stenosis and insufficiency, acute cardiac dilatation,† multiple arthritis, subsiding,* endocervicitis,* early latent syphilis, arsphenamine hepatitis, subsiding, jaundice, subsiding	Endocarditis (aortic), with rupture of cusps, abscess of interventricular wall and acute focal myocardial necrosis,* healed rheumatic endocarditis of mitral and aortic valves, with insufficiency, acute splenitis, chronic interstitial hepatitis, early portal cirrhosis, recent necroses in liver (arsphenamine?), chronic endocervicitis	Gonococci obtained from cervix, 3 blood cultures (2 ante mortem and 1 post mortem) and smear of vegetation, positive complement fixation of serum for gonococci
Malignant endocarditis (mitral),* embolic glomerular nephritis, uremia,† salpingitis,* hepatitis with jaundice, subsiding, latent syphilis (seronegative)	Autopsy not permitted	Gonococci obtained from blood culture (ante mortem), positive complement fixation of serum for gonococci

Race—Two of our 12 patients were Negroes. Thayer found the white and the Negro race equally represented in his series.

Onset of Endocarditis in Relation to Primary Infection—The relation of the onset of endocarditis to the primary infection was not known in 7 instances, but in 5 the interval could be ascertained and was found to vary from three weeks to fourteen years. There was uncertainty as to the relation in 15 of Thayer's 22 patients. Some patients were not aware of ever having had genito-urinary infection. In others the symptoms of the initial infection had subsided many years previously.

Coexisting Arthritis—Nine of our patients with gonococcic endocarditis had coexisting gonococcic arthritis. In 6 the arthritis lasted only a few days. Arthritis occurred in 31 per cent of Thayer's patients, whereas this condition was present in 68.5 per cent of the 54 patients whose cases he reviewed. Thayer's studies and our experience indicate that the clinical manifestations of arthritis usually precede those of endocarditis, but at times they may develop concomitantly. Sometimes the arthritis is migratory and subsides without apparent sequelae. At times only one joint may be involved, but more commonly in our experience multiple arthralgia occurs, followed by localization in one or two joints. When the latter develops, the affected joints show exquisite tenderness, erythema, swelling and the other characteristics of acute suppurative arthritis. Tenosynovitis is frequently associated with the arthritis. Indeed, the inflammatory reaction often is predominantly peri-articular. The joints most commonly affected in our patients were the knees, ankles and wrists.

Petechiae—Seven of our 12 patients exhibited petechiae during the course of the illness. The lesions varied in size from minute spots to areas 1 cm. in diameter. The latter occasionally exhibited central areas of necrosis. The petechiae sometimes occurred in repeated crops, but in several instances they appeared early in the course of the disease and did not reappear. Thayer observed petechiae in 7 of his 22 patients, and Stone, in 21 of his group of 77.

Other Embolic Phenomena—Evidence of arterial embolism was observed frequently at necropsy but less often clinically. In our series, 2 patients had embolism of the femoral artery, and 1 probably had cerebral embolism. There were 7 instances of acute nephritis which was regarded as being of embolic origin. Thayer observed embolic phenomena in two thirds of his patients. Stone reported embolic hemiplegia in 8 of 77 patients and other embolic manifestations in 20. It should be emphasized that embolic phenomena are extremely important when it is being ascertained whether in a given case gonococcemia is associated with endocarditis, and they are also of aid in the determination of which valves are involved. The commonest sites of lodgment

are the skin, conjunctivae, kidneys, spleen, lungs, brain and cardiac muscle

Chills—Chills occurred in all our patients. In 11 they were frequent. Chills occurred during the course of the disease in 63 per cent of Thayer's patients. Both gonococcemia without endocarditis and gonococcic endocarditis pursue a "septic course," characterized by chills, sweats, remittent or intermittent fever and other symptoms of sepsis, but when endocarditis is present the temperature rises higher, and the chills are more frequent and last longer. In our patients fluctuations in temperature of as much as from 8 to 10 degrees F commonly occurred, and in 6 instances "double peaks" were present almost daily. Horder and Gow¹³ said they regarded the daily occurrence of a temperature curve with "double peaks" as suggestive of gonococcic septicemia.

Signs of Cardiac Involvement—The pulse rate was usually rapid. The volume, of course, depended on which valve was involved. Three patients had moderate enlargement of the heart, 2 had slight enlargement and 7 had no enlargement. Most of the patients with initial involvement exhibited long, loud, harsh systolic murmurs, transmitted over a wide area. Three of these also had faint presystolic rumbles. The patients with involvement of the aortic valve exhibited the classic cardiac and peripheral signs of aortic insufficiency. The signs of progressive valvular destruction were detectable in some of our patients, and in 2 instances a diagnosis of rupture of aortic cusps was correctly made ante mortem.

Changes in the quality, intensity and transmission of the murmurs are most important in the decision as to whether a given murmur is functional, due to an old valvular lesion or due to acute endocarditis. The appearance of a diastolic murmur or an unmistakable change in quality and timing of systolic murmurs during observation of the patient is strongly suggestive of acute endocarditis.

Signs of cardiac failure when present in any of the patients in our series did not appear until the last hours or days of life, in several instances there were none.

Electrocardiograms—Electrocardiograms were made for 10 of the patients. In 2 there were no abnormalities. In 1 there was evidence of bundle branch and a fibroization block and extensive myocardial damage. In 6 patients low voltage of the QRS complex and a depressed T wave were noted, and in 4 of these patients slurring and notching of the QRS complex were exhibited. In 1 case depression of the T wave in lead I and inversion in leads II and III were noted.

¹³ Horder, Thomas, and Gow, A. E. *Essentials of Medical Diagnosis*, Baltimore, William Wood & Company, 1930, p. 624.

Duration of Endocarditis—The duration of endocarditis in our patients is estimated as varying from ten days to fourteen weeks, with an average of five and one-half weeks. It was three weeks or less in 5 instances. Peters and Horn¹⁴ reported an instance in which death occurred five days after the clinical appearance of cardiac involvement. Thayer found that the chronicity of bacterial endocarditis could be related to the etiologic agent involved, the gonococcal form occupying a midposition between the acute fulminant endocarditis associated with the hemolytic streptococcus, pneumococcus and staphylococcus and the subacute process which is usually associated with *St. viridans* and the influenza bacillus.

Blood—There was usually outspoken leukocytosis, which at times was marked. The highest leukocyte counts for our series varied from 10,500 to 53,700, with an average of 21,120. Thayer found the leukocyte count to be above 20,000 for 14 of his 22 patients, and Stone found the highest count to be above 26,000 for 18 of 37 patients.

With the progression of the disease the values for hemoglobin underwent steady and sometimes marked decline. The lowest individual estimations of the hemoglobin value for our group varied from 4 to 14 Gm. per hundred cubic centimeters of blood, with an average of 8.6 Gm. Stone found the hemoglobin value to be below "50 per cent" for 13 of 19 patients studied by him.

Renal Complications—Acute nephritis is one of the commonest complications of gonococcal endocarditis. Its development is indicated by the presence in the urine of a moderate amount of albumin, together with red blood cells, white blood cells and casts. The renal changes usually do not occur until toward the last days or weeks of the disease, but not infrequently they progress rapidly. Seven of our 12 patients were regarded clinically as having complicating acute nephritis. For 6 of these the nonprotein nitrogen content of the blood was over 80 mg. per hundred cubic centimeters. Uremia was the main cause of death in 5 instances. Thayer encountered nephritis in most of his patients, and it was present in 37 of the 85 ("proved") instances of gonococcal endocarditis reviewed by Stone. It is usually of an embolic glomerular or intracapillary type. At times the occurrence of renal infarcts, with resulting hematuria and albuminuria, may lead to confusion.

ANATOMIC OBSERVATIONS

Pericarditis was not observed in any of the patients of our series. Thayer encountered this condition post mortem in 4 and Stone in 13 instances. It was usually of a purulent type.

¹⁴ Peters, H. L., and Horn, B. Malignant Ulcerative Gonococcal Endocarditis, J. A. M. A. 102:1924 (June 9) 1934.

Areas of focal necrosis in the myocardium, sometimes amounting to true miliary abscess formation, were present in 6 of our patients. Extravasation of blood into the myocardium was seen in 1 case.

The relation of these observations to the electrocardiographic studies is interesting. For 3 of the 6 subjects exhibiting myocardial lesions at autopsy the electrocardiogram was abnormal, for 1 it was normal and for 2 none was made. Three patients with an abnormal electrocardiogram exhibited no evidence of structural change in the myocardium at postmortem examination. There was slight dilatation of the cardiac chambers in a few instances, but there was little if any cardiac hypertrophy. These observations are in accord with those of Thayer.

The valvular involvement consisted of varying degrees of erosion and ulceration of the leaflets, causing rupture of cusps in 2 instances. The vegetations were large, friable and grayish yellow and were composed of fibrin, leukocytes and gonococci. The lesions were confined to the valves on the left side of the heart in our 10 subjects. Five had mitral lesions, 4 had aortic lesions and 1 showed both aortic and mitral involvement. In the combined material of Kirkland and Thayer, based on 93 reports of cases, including necropsy observations, 41 of the patients exhibited aortic lesions, 20, mitral lesions, 7, pulmonic lesions, 1, tricuspid lesions, and 24, involvement of more than one valve. Twelve of the last-mentioned group had mitral and aortic endocarditis. Although Thayer encountered evidence of a preexisting chronic valvular lesion in 20 per cent of his patients, it was present in only 1 of our patients.

In 2 subjects embolic pneumonia was present and in 2 interstitial pancreatitis.

The spleen was usually large, as a result of acute splenitis, and in 6 instances there were infarcts. In 7 the spleen weighed over 290 Gm., and in 1, 940 Gm. The average weight was 379 Gm.

The liver in 7 instances weighed over 1,700 Gm., the average weight was 1,842 Gm. All the patients showed hepatic congestion, 3, central necrosis, and 1, marked cirrhosis (syphilitic), with small areas of infarction. One patient exhibited recent areas of necrosis (arsphenamine¹⁵), chronic interstitial hepatitis and early portal cirrhosis. Two patients had ascites. Blumer and Nesbit¹⁵ have recently reported on a patient with gonococcic endocarditis in whom acute hepatitis and portal cirrhosis with jaundice occurred. Jaundice was present in 5 of our patients (including the twelfth, who was not examined post mortem). The jaundice was believed to be due to syphilitic cirrhosis in 1 instance and to arsphenamine hepatitis in another. In the remainder it was attributed

¹⁵ Blumer, George, and Nesbit, Robert R. A Case of Gonococcal Septicaemia with Endocarditis and Hepatitis, *Internat. Clin.* 4:44 (Dec.) 1936.

to congestion and necrosis. The changes in the liver which are associated with gonococcic endocarditis are impressive clinically and at necropsy and are worthy of further investigation.

Glomerular nephritis was present in 8 patients, and renal infarcts were present in 2. Three patients had intracapillary glomerular nephritis, 3 had embolic glomerular nephritis, 1 had acute glomerular nephritis and 1 had acute focal glomerular nephritis.

Causes of Death—Although it is difficult to decide in each instance which of the several possible factors was responsible, the probable causes of death in our patients are listed as follows: acute heart failure in 6 instances, uremia in 5 and cerebral embolism in 1. The patients with cardiac failure usually died a few hours after the development of the first distinct manifestations of this condition. The uremia ordinarily progressed rapidly.

DIAGNOSIS

The difficulty in recovering the gonococcus by blood culture has constituted the chief obstacle to the clinical recognition of gonococcic endocarditis. The bacteriologic diagnostic criteria have been summarized by Solomon and his associates.⁹ Various mediums and technics have been recommended. We employed for blood culture dextrose agar and yeast broth to which ascitic fluid had been added, and the cultures were incubated under increased carbon dioxide tension. The organisms were differentiated by fermentative and agglutinative reactions. Gonococcus complement fixation tests were performed with the serum of 2 patients. The reactions were positive.

The data which established the diagnosis of gonococcic endocarditis in our patients may be seen in table 1. Blood cultures were made ante mortem in all instances, and in cases 2 to 4, 6, 7 and 9 to 12 gonococci were found. In cases 2, 3, 7, 9 and 11 gonococci were also found in the smears made from the vegetations at necropsy. In case 5 gonococci were not recovered by ante mortem blood culture but were found by studies of smears and cultures of the vegetation on the aortic valve. In case 8 seven blood cultures remained sterile, but gonococci were found post mortem in smears of material from the aortic valve and from the cervix. In case 1 gonococci were obtained from the urethra and the knee. In this instance three blood cultures remained sterile, and a post-mortem examination was not made. However, when the entire clinical picture and the course are considered, there is no doubt that the patient had gonococcic endocarditis.

PROGNOSIS

Practically all the authenticated cases of gonococcic endocarditis which have been reported have terminated fatally. However, Thayer,⁴ who said he regarded recovery as rare, mentioned reports of recovery

published by Silvestrini, Withington, Dieulafoy, Maifan and Debré Periy¹⁶ and Newman¹ have also reported instances of recovery. Periy's patient was a young man in whom urethritis developed three months preceding his main illness, which ran a septic course. While he was under observation a distinct diastolic murmur developed over the pulmonic area, and there was clearcut evidence of frequent pulmonary embolism. Gonococci were cultured from the blood. The patient was treated with repeated small blood transfusions and general supportive measures. He recovered after a two month illness. A report¹⁷ made three years later related that the patient had led a normal life and had indulged in vigorous physical activities without apparent difficulty. Examination of the heart revealed nothing of note except a diastolic murmur well localized in the pulmonic area. It seems that this case constitutes an example of healed gonococcic endocarditis. Most of the other reports of recoveries have been questioned. Jagic and Schiffner¹⁸ expressed the opinion that patients with mild involvement not infrequently recover. These opinions can be defended only as opinions.

DIFFERENTIAL DIAGNOSIS

Many conditions may be confused with gonococcic endocarditis, chief of which are gonococcemia without endocarditis, nongonococcic bacterial endocarditis, acute rheumatic fever, meningococcemia, miliaary tuberculosis, typhoid, malaria and pyelophlebitis. Of these, gonococcemia and nongonococcic acute endocarditis cause the most confusion. Some of the points in the differential diagnosis will be considered presently. It should be emphasized, however, that the significant findings which indicate the presence of gonococcic endocarditis are the signs of progressive involvement of the cardiac valves in a patient with gonococcemia.

Gonococcemia Without Endocarditis—One frequently has difficulty in determining whether a patient with severe focal gonococcic infection and gonococcemia has endocarditis, as the clinical pictures may be similar.

I have reviewed the hospital records of 5 patients with gonococcic infection and gonococcemia in whom no involvement of the cardiac valves was present, and the important data are summarized in table 2. Briefly, it may be said that the clinical picture of gonococcemia without endocarditis differs from that of gonococcic endocarditis in the following respects. In gonococcemia without endocarditis the chills are fewer

16 Perry, M. W. Gonorrheal Endocarditis with Recovery. A Case Report, *Am J M Sc* **179**:599 (May) 1930.

17 Perry, M. W. Further Note on a Case of Gonorrheal Endocarditis with Recovery, *Am J M Sc* **185**:394 (March) 1933.

18 Jagic, N., and Schiffner, O. Ueber gonorrhoeische Herzerkrankungen, *Med Klin* **16**:976 (Sept) 1920.

and occur at longer intervals, the fluctuations in temperature are not so great and usually do not occur on consecutive days, petechiae are fewer and do not appear in repeated crops, cardiac murmurs are systolic rather than diastolic, are not intense or harsh and do not show significant alterations, and embolic phenomena are absent. All our patients recovered. However, it should be emphasized that these differences usually are impressive only after prolonged and close observations and that the decision as to whether or not endocarditis is present in a patient with gonococcemia is usually difficult.

In 1934 Friedberg¹⁹ reviewed 11 instances of gonococcemia without apparent endocarditis and found that 6 of the patients were described as appearing acutely ill, 9 had chills, 8 had arthritis, 9 had systolic murmurs and 8 had maculopapular eruptions. The temperature reached 103 F or above in all instances. No embolic phenomena were observed.

TABLE 2—*Summary of Clinical Data for Five Patients With Gonococcemia Without Endocarditis*

Case	Appearance	Average Daily Maximum Temperature, F	Chills	Purulent Arthritis	Cardiac Murmurs	Petechiae	Embolic Phenomena	Blood Culture	Gonococci Demonstrated in Primary Genito- Urinary Focus
1	Acutely ill	104.0	0	0	Soft systolic	0	0	+	+
2	Acutely ill	102.5	0	+	Soft systolic	0	0	+	0
3	Acutely ill	103.5	Many	+	Soft systolic	Few	0	0	+
4	Acutely ill	103.0	2	+	Soft systolic	Many	0	+	+
5	Acutely ill	104.0	4	+	Soft systolic	0	0	+	+

Acute Bacterial (Nongonococcic) Endocarditis—In this group there is no history of a primary focus of gonococcic infection (e. g., urethritis or involvement of joints or tendons), and usually some other type of infectious focus (e. g., lymphangitis, pneumonia, meningitis or osteomyelitis) is demonstrable. Blood cultures conclusively differentiate the conditions. The meningococcus is the one organism commonly encountered in blood cultures which may lead to confusion.

TREATMENT

The types of treatment which have been employed in gonococcic endocarditis are innumerable. The multiplicity and variety attest to their ineffectiveness. There is one form of treatment which appears promising—fever, particularly when induced by means of the Kettering hypertherm. This machine is to be commended because it is constructed so as to permit close watch of the patient, and its temperature and

¹⁹ Friedberg, Charles K. Gonococcemia with Recovery. Report of Four Cases, *Am J M Sc* **188** 271 (Aug) 1934.

humidity are kept at a fairly constant level. The marked sensitivity of the gonococcus to heat has been determined on many occasions *in vitro*. Simpson²⁰ and Desjardins and his associates²¹ have reported cures in the majority of cases of gonococcic infection in which treatment was given with fever in the Kettering hypertherm. Kendell and Simpson²² have demonstrated by means of thermocouples inserted in various parts of the body that the temperature of the tissues beneath the skin is elevated to essentially the same degree as that of the body surfaces. Consequently, there is reason to hope that gonococci in the cardiac valves may be destroyed as readily by heat as those in other sites, assuming that heat is the effective factor and that the patient's condition will permit the induction of the necessary amount of fever. Treatments in the Kettering hypertherm were used in case 10. They were not instituted, however, until evidence of severe hepatic and renal damage had developed. Death occurred from uremia after the second treatment. Treatment of this patient rendered antemortem blood cultures sterile, and at necropsy organisms could not be demonstrated in the vegetation on the cardiac valve by either smear or culture. Another patient with gonococcemia and suspected endocarditis, who was not included in this series, recovered after this form of treatment. A complete report on these patients has been made.²³

The efficacy of sulfanilamide in the treatment of gonococcic urethritis²⁴ obviously warrants a trial of this drug, either alone or in conjunction with hyperthermia, in gonococcemia with or without gonococcic endocarditis.

SUMMARY

Gonococcic endocarditis constituted 26 per cent of all instances of acute bacterial endocarditis in patients admitted to the Vanderbilt University Hospital during the past twelve years. It was noted in 0.7 per cent of 1,719 autopsies performed during this period. It occurred in all age groups and was more frequent in men. Its mode of onset was variable, and symptoms appeared from a few days to several years after the primary infection. The onset was sometimes insidious, consisting of generalized aching, malaise and moderate fever for several days. In other patients there occurred in a period of a few hours high

20 Simpson, Walter M. Artificial Fever Therapy of Syphilis and Gonococcic Infections, *New York State J. Med.* **36** 1290 (Sept. 15) 1936.

21 Desjardins, A. U., Stuhler, L. G., and Popp, W. C. Fever Therapy for Gonococcic Infections, *J. A. M. A.* **106** 690 (Feb. 29) 1936.

22 Kendell, W., and Simpson, W. M. Personal communication to the author.

23 Williams, Robert H. Gonococcal Endocarditis Treated with Artificial Fever, *Ann. Int. Med.* **5** 1766 (June) 1937.

24 Dees, John E., and Colston, J. A. C. The Use of Sulfanilamide in Gonococcic Infection, *J. A. M. A.* **108** 1855 (May 29) 1937.

fever, chills, petechiae and articular pains. Acute polyarthritides was usually the first focal manifestation of generalized gonococcal infection. Petechiae were frequently present. They usually occurred early in the disease and frequently recurred in showers. It is noteworthy that large petechiae with necrotic centers are suggestive of endocarditis. Renal complications, frequently embolic, were commonly present. Chills occurred in all cases and sometimes were numerous. The temperature usually showed marked daily fluctuations. During the course of the illness the heart was ordinarily not enlarged, but acute dilatation frequently occurred as a terminal event. Characteristic signs of valvular disease appeared in every instance during the illness. Myocarditis sometimes occurred. The liver and spleen were often enlarged, and jaundice was present in 5 instances. Marked leukocytosis and moderate or severe anemia occurred. The urine frequently contained moderate amounts of albumin, red blood cells, white blood cells and casts. Uremia was a common development and was the main cause of death in 42 per cent of our patients. The duration of the endocarditis varied from a few days to several months. The average duration was five weeks.

A correct diagnosis of gonococcal endocarditis can be established only after close clinical observation and careful bacteriologic studies. Every attempt should be made to obtain the organisms from the primary focus and from any joint or tendon involved. Frequently repeated cultures on special mediums are often necessary in order to recover gonococci from the blood. In every case listed in table 1 the diagnosis of gonococcal endocarditis was established ante mortem.

The prognosis of gonococcal endocarditis has always been regarded as grave, and our experience confirms this attitude. Electropylrexia and a recent development in chemotherapy (sulfanilamide) seem to offer some therapeutic promise.

CONCLUSIONS

Gonococcal endocarditis is not a rare disease, since it was present in 26 per cent of the patients with bacterial endocarditis (acute and subacute) and in 0.7 per cent of all patients coming to autopsy at the Vanderbilt University Hospital.

Careful observation of the patient and thorough laboratory examinations will usually lead to a correct diagnosis.

Acute nephritis is one of the commonest and most significant complications of gonococcal endocarditis.

Uremia and acute heart failure are the usual causes of death.

The prognosis is grave. The results following the use of the Kettering hyperthermia and the apparent effectiveness of sulfanilamide in gonococcal infections are sufficiently encouraging to warrant therapeutic trial.

MITRAL STENOSIS

A CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC OBSERVATIONS

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AND

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In recent years there has been a tendency to minimize the effects of valvular lesions and to regard infection of the myocardium as almost the sole determining factor in the course of rheumatic heart disease. This point of view¹ represents a reaction to the older, purely mechanical conception of valvular disease, and it may have been carried too far by some. The truth lies between the two extremes. As White² has pointed out

With chronic healed valvular disease there need not be any trace of previous infection in the perfectly healthy muscle. Eventually the myocardium may become exhausted and fail. In other words, it is the valve lesion, if well marked, and not the myocardial disease that eventually causes failure and death.

This profound effect of valvular lesions on the dynamics of the circulation is demonstrated in many ways. Fluoroscopic examination, for instance, shows significant changes in the size of the individual cardiac chambers to be regularly associated with certain valvular lesions, e g, enlargement of the left auricle in mitral stenosis. Electrocardiography demonstrates the specific effect of each valvular lesion on the heart hardly less well than fluoroscopy. In fact, certain electrocardiographic changes appear with such regularity that the electrocardiogram can be used as an aid in the differential diagnosis of valvular lesions. The present study aims to analyze the electrocardiographic changes characteristic of the most frequent valvular lesion, mitral stenosis, and to ascertain their diagnostic value by determining their frequency.

METHOD

To eliminate any possible doubt as to the correctness of the diagnosis, this study was limited to fatal cases in which postmortem data were available.

From the Cardiographic Laboratory and the Medical Services of the Mount Sinai Hospital.

1 Rothschild, M A, Kugel, M A, and Gross, L. Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease, *Am Heart J* 9 586, 1934.

2 White, Paul D. Heart Disease, New York, The Macmillan Company, 1931, pp 231 and 487.

Reports of a series of 113 consecutive cases of mitral stenosis of rheumatic etiology in which the patients were observed in the wards of the Mount Sinai Hospital between the years 1925 and 1936 were collected, and the accompanying electrocardiograms, 265 in number, were analyzed. Each electrocardiogram was examined as to standardization, and only technically perfect tracings were included in this series. Only cases in which the condition was definitely described as rheumatic heart disease in the autopsy report were investigated. Great care was taken to exclude any cases in which mitral stenosis was associated with any other pathologic condition, cardiac or otherwise, which was likely to have exerted an effect on the electrocardiogram. Many cases of arterial hypertension associated with mitral stenosis were thus excluded. Moreover, an associated condition such as a large hydrothorax or perforated carcinoma of the stomach with air under the left dome of the diaphragm led to the elimination of the case from the series because of the possible effect on the electrical axis. The remaining 113 cases were arranged in eight groups:

- 1 Cases of mitral stenosis with or without mitral insufficiency and uncomplicated by disease of any other valve
- 2 Cases of disease of the mitral valve associated with tricuspid stenosis with or without tricuspid insufficiency
- 3 Cases of disease of the mitral valve associated with tricuspid insufficiency without tricuspid stenosis
- 4 Cases of disease of the mitral valve associated with aortic stenosis with or without aortic insufficiency
- 5 Cases of disease of the mitral valve associated with aortic insufficiency without aortic stenosis
- 6 Cases of lesions of three valves—mitral, tricuspid and aortic
- 7 Cases of pure mitral insufficiency without mitral stenosis
- 8 Cases of mitral insufficiency associated with aortic insufficiency

The electrocardiograms, varying in number from 1 to 12 in each case, were carefully analyzed as to the characteristic signs of mitral stenosis, namely, changes in the size and shape of the auricular complex (P wave) and changes in the ventricular complex resulting from preponderance of either ventricle. Certain other electrocardiographic signs—the duration of the PR interval, the initial ventricular deflection (Q wave), the voltage and duration of the main ventricular deflection (QRS) and the direction of the final ventricular deflection (T wave)—also were investigated.

Besides, it was determined from the autopsy report in each case which ventricle predominated in size, and this anatomic relationship was then compared with the electrocardiographic findings of ventricular preponderance in the same case. Lastly, the relative sizes of the left and right auricles were compared with the changes in the auricular complex of the electrocardiogram, and correlation was attempted.

RESULTS

Changes in the P Wave—The normal P wave is an upright deflection, 1 to 2.5 mm high and not over 0.1 second wide. One of the characteristic electrocardiographic signs of mitral stenosis is an increase in the height and width of the P wave.

Lewis³ has described it as follows "The summit P has an exaggerated amplitude amounting frequently to two, three, or even four scale divisions, it is often broad, flattened and notched in the center"

Notching of the P wave, especially notching near the peak, is sometimes found in association with other conditions and at times when there is no abnormality. With no other condition, however, is marked notching found so frequently as with mitral stenosis. The higher the P wave, usually the more marked the notching. Most frequently the notching was found near the peak of the P wave, either on the downstroke or, less often, on the upstroke. Notching on the downstroke near the base line of a P wave which was not diphasic was found only rarely. In 61 of our series of 69 cases of mitral stenosis with regular rhythm the P wave was notched. In 14 of 16 cases of uncomplicated mitral stenosis with regular sinus rhythm there was notching of the P wave in one or more leads, and in 6 of these cases there was, besides, widening of the P wave in at least one lead (chart 1 *A* and *B*). The average height of the P wave in lead II in these 16 cases was 1.63 mm, which is well within the normal range. In only 4 of the 16 cases was the P wave higher than 2 mm, and in 4 more cases it was 2 mm high. Marked increase in the amplitude of the P wave was therefore not frequent in the cases of uncomplicated mitral stenosis. When it did occur, however, an anatomic explanation for it could be obtained by comparison of the postmortem observations with the electrocardiogram.

Such a comparison revealed an interesting relationship between hypertrophy of the auricles and the height of the P wave. In half the cases of uncomplicated disease of the mitral valve there was hypertrophy of the right auricle besides hypertrophy of the left auricle, and in all these cases there was a high P wave, of from 2 to 3.5 mm, or auricular fibrillation. In the remaining cases, on the other hand, in which only the left auricle was hypertrophic, the P wave was of normal height, and in no case was there auricular fibrillation. It may be inferred that a marked increase in the height of the P wave with notching is pathognomonic of enlargement of both the right and the left auricle. Observation in a larger series of cases, however, appears necessary before this conclusion can be definitely accepted.

Meanwhile, another observation seems to suggest the same conclusion. Marked increase in the amplitude of the P wave was much more frequent when disease of the mitral valve was complicated by disease of the tricuspid valve. The highest P waves, of 3.5 mm and more, were observed in cases of mitral stenosis associated with tricuspid

³ Lewis, Thomas. *Clinical Electrocardiography*, London, Shaw & Sons, Ltd, 1928, p. 108.

stenosis These same P waves were usually wider and more markedly notched This increase in the size of the P wave is probably explained by the fact that the combination of disease of the mitral and of the tricuspid valve produces marked enlargement of both auricles, whereas uncomplicated disease of the mitral valve primarily affects only the left auricle An analysis of our 21 cases of disease of the mitral and tricuspid valves shows 4 cases in which only the left auricle was hypertrophic while the right auricle was normal The electrocardiograms in 3 of these 4 cases were characterized by a P wave of normal height (in the fourth case there was auricular flutter), and in 2 there was no notching of the P wave In the remaining 17 cases of mitral and tricuspid valvular disease, on the other hand, both auricles were found

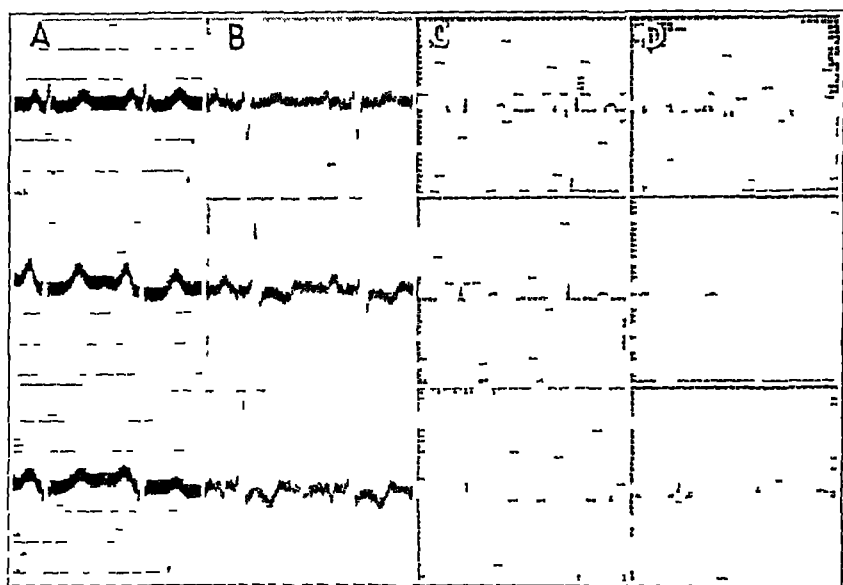


Chart 1—*A*, mitral stenosis with mitral insufficiency Note the notched, high and broad P waves, the normal voltage of QRS and the absence of signs of preponderance *B*, tight mitral stenosis without mitral insufficiency Note the notched P waves (inverted in the third lead), the PR intervals of 0.23 second and the right ventricular preponderance, with inversion of T_2 and T_3 Although at post-mortem examination the left ventricle was atrophic, the voltage of R in the third lead was 16 mm, at the upper border of normal *C*, mitral insufficiency without preponderance Note the normal P waves and the tendency to left ventricular preponderance, viz., an S wave without an R wave in lead III and R_1 not taller than R_2 *D*, mitral insufficiency without stenosis Note the almost normal P waves, with only slight notching in lead II, and the absence of signs of preponderance

hypertrophic at postmortem examination Comparison of the electrocardiograms revealed an illuminating difference in the appearances of the P wave With but 2 exceptions the P wave was higher than in the cases in which there was hypertrophy of only the left auricle, and in every instance it was notched This difference in height and notching

of the P wave may perhaps be caused by a summation of electrical effects produced by the simultaneous contraction of the two hypertrophic auricles, but this group of cases is of course too small to permit the drawing of any definite conclusions.

Besides, it is well to remember at this point that an absolutely constant relation between the height of the P wave and the degree of auricular hypertrophy can never be expected, just as there is no constant relation between the height of the QRS complex and the degree of ventricular hypertrophy. A failing heart is known often to show low voltage of the ventricular complex. By the same token, the voltage of the auricular wave must be influenced by variations in the func-

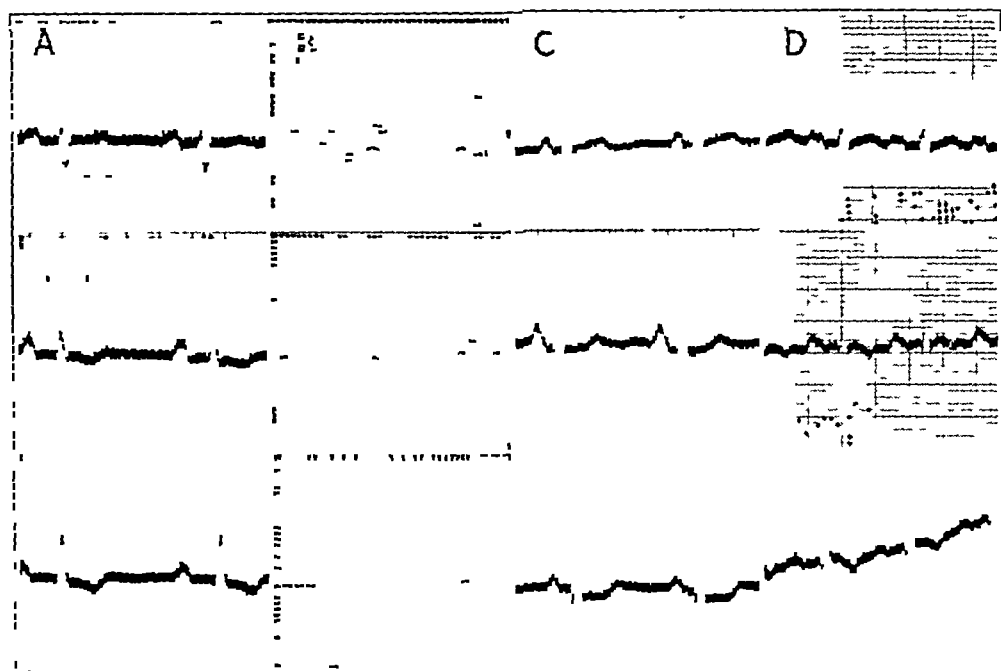


Chart 2—A, mitral stenosis with mitral insufficiency and tricuspid stenosis with tricuspid insufficiency. Note the notched, broad P waves, the PR intervals of 0.23 second and the right ventricular preponderance, with inversion of T_2 and T_3 . B, mitral stenosis with mitral insufficiency and tricuspid stenosis with tricuspid insufficiency. Note the notching of the P waves and the tendency to right ventricular preponderance. C, mitral stenosis and tricuspid insufficiency without tricuspid stenosis. Note the notched, high and broad P waves and the right ventricular preponderance. D, mitral stenosis with mitral insufficiency and tricuspid insufficiency without tricuspid stenosis. Note the notched, broad P waves and the right ventricular preponderance, with inversion of T_2 and T_3 .

tional status of the auricular musculature. It is no wonder, therefore, that marked auricular hypertrophy is occasionally found to be associated with a P wave of normal height. As a matter of fact, it is surprising that such exceptions are not more frequent.

A still more difficult problem was the search for electrocardiographic signs of auricular preponderance. This search failed completely. We

found 4 cases in our series in which there was hypertrophy of the right auricle but a normal left auricle. The P wave in the electrocardiograms in these cases was no different from that in 16 cases of hypertrophy of only the left auricle, with a normal right auricle. Inversion of P_3 occurred with the same frequency with hypertrophy of either the right or the left auricle.

When the left auricle showed a rheumatic lesion at necropsy, the P wave of the electrocardiogram appeared no different from that in cases in which the auricular wall was not invaded, and notching, in particular, was no more marked. This subject deserves further investigation, however, as the number of cases of auriculitis included in this study was too small to warrant the drawing of definite conclusions.

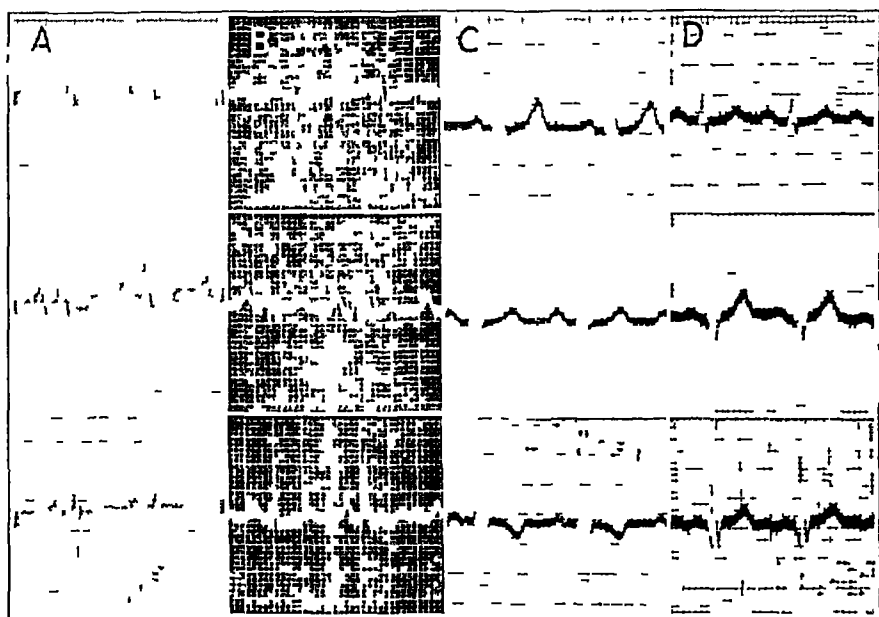


Chart 3—*A*, mitral stenosis (slight) and aortic stenosis. Note the slightly notched P waves and the left ventricular preponderance, with inversion of T_1 and T_2 . *B*, mitral stenosis ("button-hole" type) with mitral insufficiency and aortic stenosis (slight). The left ventricle was very small. Note the notched, high P waves, the normal voltage of QRS and the right ventricular preponderance. *C*, mitral stenosis with mitral insufficiency and aortic insufficiency. The blood pressure was 130 systolic and 45 diastolic. Note the slightly notched, broad P waves, the high voltage of QRS and the left ventricular preponderance. The duration of QRS is 0.1 second. *D*, mitral stenosis with mitral insufficiency and aortic insufficiency. The blood pressure was 114 systolic and 70 diastolic. Note the slightly notched P waves, inverted in lead III, the normal voltage of QRS and the absence of preponderance.

In the group of cases of mitral stenosis with aortic insufficiency (chart 3 *C* and *D*) the average height of the P wave was no greater than with pure mitral stenosis. While some notching was found in all cases of this group, no P wave was higher than 2.5 mm. The contrast

between the findings in this last group and those in the cases of mitral stenosis with disease of the tricuspid valve reflects the fact that disease of the aortic valve does not directly affect the size of either auricle, whereas disease of the tricuspid valve leads to enlargement of the right auricle, in addition to enlargement of the left auricle produced by stenosis of the mitral ostium

A still more striking contrast was found in the comparison of the P waves in cases of mitral insufficiency (chart 1 *C* and *D*) with those in cases of mitral stenosis (chart 1 *A* and *B*) Widening of the P wave was rarely found with mitral insufficiency, and notching was observed

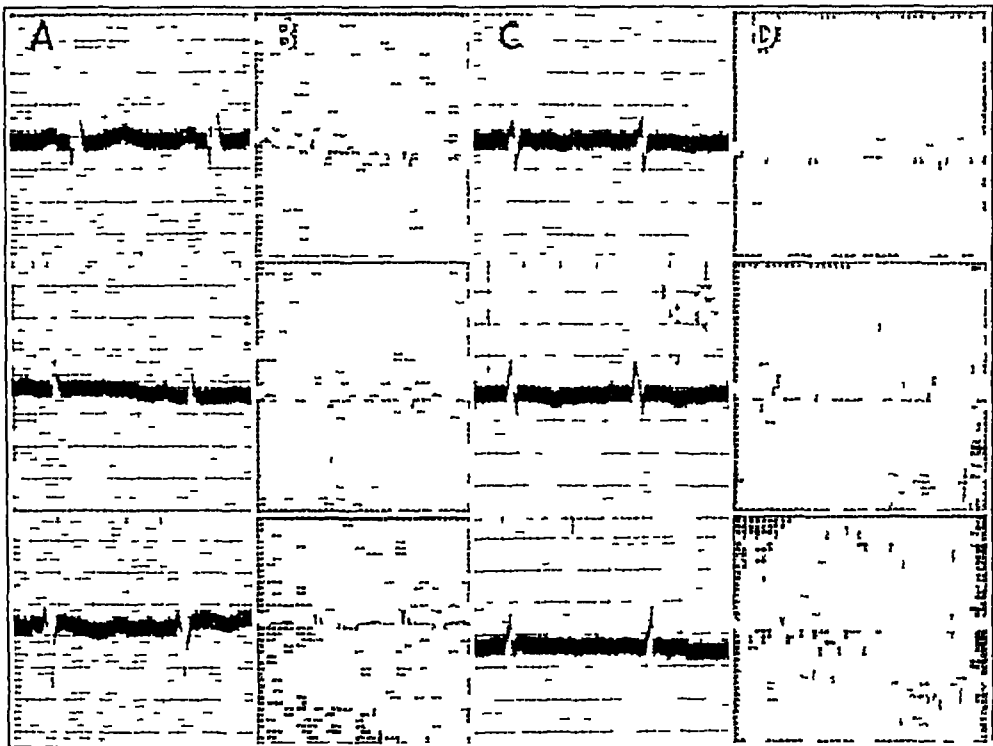


Chart 4—*A*, aortic insufficiency and mitral insufficiency without stenosis The blood pressure was 120 systolic and 60 diastolic Note the notched P waves of normal height Observe the fairly high voltage of QRS portrayed and the left ventricular preponderance *B*, aortic insufficiency and mitral insufficiency without stenosis Pericardial effusion was noted The blood pressure was 145 systolic and 95 diastolic Note the normal P waves, the duration of QRS (0.14 second), the low voltage of QRS and the left ventricular preponderance *C* and *D* (the same case), three lesions mitral stenosis with insufficiency, tricuspid stenosis with insufficiency and aortic stenosis with insufficiency Note the change from right ventricular preponderance to left ventricular preponderance, the auricular fibrillation in *C* and the notched P waves in *D* In *D* the prolongation of the PR interval to 0.28 second and the inversion of T_1 were due to the administration of digitalis

in only half the cases The addition of aortic insufficiency to mitral insufficiency did not affect this relationship The notching when present

was less marked than in the other groups, and the average amplitude of the P wave was slightly lower (chart 4 *A* and *B*)

Occurrence of Auricular Fibrillation and Auricular Flutter—In 4 of the 19 cases of pure mitral stenosis, auricular fibrillation occurred. When disease of the tricuspid valve was associated with mitral stenosis, auricular fibrillation was more frequent (8 of the 21 cases). The association of aortic insufficiency with mitral stenosis, on the other hand, did not affect the frequency of auricular fibrillation. In 4 of the 19 cases there was auricular fibrillation—the same proportion as in the cases of uncomplicated mitral stenosis and mitral insufficiency.

In the small group of 7 cases of aortic and mitral stenosis, auricular fibrillation occurred 3 times and auricular flutter once. Auricular fibrillation was most frequent in the group of cases of mitral stenosis with disease of the tricuspid and aortic valves, in 15 of the 32 cases this irregularity was noted. In 15 cases of mitral insufficiency without stenosis, on the other hand, not a single instance of auricular fibrillation was found, and it made no difference whether aortic insufficiency complicated mitral insufficiency or not.

Auricular flutter occurred in only 3 of the 113 cases, each time in a case of mitral stenosis complicated by disease of the aortic or tricuspid valve or disease of both valves. This group is too small to permit the drawing of any conclusions from it.

Ventricular Preponderance—This electrocardiographic sign shows more clearly than any other the profound effect which a valvular lesion exerts on the dynamics of the heart. In this study the width of the mitral ostium and the other associated valvular lesions proved to be the two principal factors which determined ventricular preponderance.⁴

To determine whether the degree of stenosis had an effect on the signs of ventricular preponderance in the electrocardiogram, we examined all necropsy records and arranged the cases in two groups, those in which there was tight stenosis and those in which there was moderate or slight stenosis. In all the cases of tight stenosis of the mitral valve there was marked hypertrophy of the right ventricle, with the left ventricle smaller than the right. In general, in the cases of mod-

4 Right ventricular preponderance was the diagnosis made when lead I had no R wave or but a small one, with the downward deflection larger than R₁, in addition, R₃ had to be taller than R₂. Left ventricular preponderance was the diagnosis made when lead III had no R wave or only a small one, with the downward deflection larger than R₃, in addition, R₁ had to be taller than R₂. A tendency to right ventricular preponderance was the diagnosis made when there was a low R wave in lead I, with the downward deflection larger than R₁ but with R₃ not taller than R₂. A tendency to left ventricular preponderance was the diagnosis made when there was a low R wave in lead III, with the downward deflection larger than R₃ but with R₁ not taller than R₂.

erate or slight stenosis, on the other hand, less marked hypertrophy of the right ventricle and varying degrees of hypertrophy of the left ventricle were noted. The electrocardiograms in these two groups were then compared and they revealed a significant difference. In only 8 of our 18 cases of uncomplicated mitral stenosis, with or without mitral insufficiency (table 1), that is, in about one-half the cases, definite right ventricular preponderance was noted. Without exception they were cases of the "button-hole" type, with tight stenosis of the mitral valve. In cases in which only moderate narrowing of the mitral ostium and mitral insufficiency were noted there was usually no preponderance or tendency to right ventricular preponderance. It is to be remembered that this study is limited to necropsy material. Of the large number of cases of earlier mitral stenosis with which the clinician comes in contact, there is a much smaller proportion in which such marked narrowing of the mitral ostium is likely to be present. Right ventricular preponderance, therefore, will be correspondingly less frequent in clinical cases. One fact stands definitely established as a result of our investigation. Ventricular preponderance depends on the degree of stenosis, the tighter the stenosis, the more definite the right ventricular preponderance. In no case of uncomplicated mitral stenosis with or without mitral insufficiency was there left ventricular preponderance.

Next, the cases of disease of the mitral and tricuspid valves were investigated. Here the findings were more uniform than in cases of uncomplicated disease of the mitral valve. Besides the stenosis of the mitral ostium, a second factor was found to be operative in these cases which tended to swing the balance of the ventricles in the same direction, toward right ventricular preponderance. This second factor was the associated lesion of the tricuspid valve. In all these cases marked hypertrophy of the right ventricle was noted. In the great majority (16 of 21 cases), therefore, right ventricular preponderance was noted, while in 3 more cases there was a tendency to right ventricular preponderance (table 1).

Outright left ventricular preponderance was never found in a case of mitral stenosis with or without mitral insufficiency unless it was complicated by aortic valvular disease. When this complication existed, particularly when aortic insufficiency as well as mitral stenosis was present, this factor tended to swing the balance of the ventricles in the opposite direction, toward left ventricular preponderance. In half these cases there was left ventricular preponderance, with either no preponderance or right ventricular preponderance noted in the other half (table 1). Comparison with the pathologic and clinical pictures usually revealed that the preponderance depended on the extent of the leak in the aortic valve. Tight mitral stenosis complicated by moderate aortic insufficiency (without a high pulse pressure) often was asso-

ciated with right ventricular preponderance. In all the cases of marked aortic insufficiency with high pulse pressure, however, there was left ventricular preponderance, whether the associated mitral stenosis was slight or marked. In other words, aortic insufficiency outweighed mitral stenosis in producing ventricular preponderance. Aortic stenosis, on the other hand, had a much less marked effect on ventricular preponderance than aortic insufficiency, and in only 1 of the 7 cases of this type was there left ventricular preponderance (table 1).

A mixed picture was presented by the group of cases of mitral stenosis with aortic and tricuspid valvular disease (table 1). In 13 of

TABLE 1—Data Regarding One Hundred and Th

Number of Cases	Valvular Lesion	Average Age	Average Height, Mm			Incidence of Inversion of P ₃	Incidence of Auricular Fibrillation	Incidence of Auricular Flutter	Incidence of Notched P Waves		Average PR Interval, Sec
			P ₁	P ₂	P ₃				Yes	No	
19	Mitral stenosis with or without mitral insufficiency	33	1.25	1.63	0.42	3	4	0	14	2	0.17
8	Mitral stenosis and tricuspid stenosis with or without tricuspid insufficiency	34	1.62	2.62	1.16	0	2	1	5	1	0.18
13	Mitral stenosis and tricuspid insufficiency without tricuspid stenosis	38	1.14	2.11	0.92	2	5	0	7	2	0.18
7	Mitral stenosis and aortic stenosis with or without aortic insufficiency	44	0.70	1.80	1.00	1	3	1	4	0	0.17
19	Mitral stenosis and aortic insufficiency without aortic stenosis	32	1.25	1.64	0.86	5	4	1	14	0	0.18
32	Three lesions: mitral stenosis with aortic and tricuspid valvular lesions	29	1.36	1.87	0.53	5	14	1	17	3	0.19
8	Mitral insufficiency, pure	12	1.13	1.62	0.63	0	0	0	4	4	0.16
7	Mitral insufficiency and aortic insufficiency	32	1.00	1.25	0.36	3	0	0	4	3	0.17

* One case was rejected.

† Besides four with a complete change of preponderance.

the 32 cases there was right ventricular preponderance, reflecting the dominant effect of disease of the tricuspid valve. In 6 cases there was left ventricular preponderance, and in these cases the lesion of the aortic valve exceeded that of the mitral and tricuspid valves in extent and dynamic effect. In 4 of the remaining 13 cases there was varying preponderance, no preponderance in 1 electrocardiogram and right or left ventricular preponderance in another electrocardiogram or even a complete change from right to left ventricular preponderance in successive tracings. These variations reflect the fact that changes in the interplay of the lesions may occur and may even be reversible.

Reviewing all 93 cases of mitral stenosis, pure or complicated with other valvular lesions, we find that in 45, i. e., about half, there was right ventricular preponderance, in 11 there was noted a tendency to right ventricular preponderance. In only 15 cases, all of them

cases of mitral stenosis with disease of the aortic valve, was there left ventricular preponderance, in 5 there was noted a tendency to left ventricular preponderance, and in 17 there was no ventricular preponderance

Mitral insufficiency without stenosis revealed itself as a valvular lesion with a less marked effect on ventricular preponderance than mitral stenosis. If at all, mitral insufficiency tends to change the balance toward preponderance of the left ventricle. In 1 of the 8 cases of pure mitral insufficiency there was left ventricular preponderance, in 3 there was a tendency to left ventricular preponderance, in only 1 was there

teen Fatal Cases of Disease of the Mitral Valve

Incidence of Prolonged PR Interval	Incidence of Q Wave		Average Duration of QRS, Sec	Incidence of Wide QRS	Average Highest Voltage, Millivolts	Incidence of High Voltage (16 Millivolts or More)	T Waves							Right Ventricular Preponderance	Tendency to Right Ventricular Preponderance	Left Ventricular Preponderance	Tendency to Left Ventricular Preponderance	No preponderance	Number of Tracings
	Q ₁	Q ₃					All Up	T ₁ Inverted	T ₁ and T ₂ Inverted	T ₃ Inverted	T ₃ Biphasic	T ₂ and T ₃ Inverted	All Inverted						
2	2	12	0.07	2	10	1	9	0	0	7	1	2		8	3	0	1	6*	41
1	1	5	0.07	0	10	0	5	0	0	1	0	2		6	1	0	0	1	14
2	1	9	0.08	1	10	0	3	0	0	5	3	2		10	2	0	1	0	40
0	0	5	0.07	0	8	0	4	0	1	0	0	1	1	3	1	1	0	2	13
2	5	11	0.08	4	14	5	9	1	3	3	0	3		4	1	8	1	5	37
5	6	16	0.08	2	12	6	10	5	2	6	0	9		13	3	6	2	4†	86
0	2	6	0.06	0	9	1	7	1	0	0	0	0		0	1	1	3	3	23
1	3	3	0.10	3	11	1	1	2	0	3	0	0	1	0	0	4	0	3	11

a tendency to right ventricular preponderance, in none was there actual right ventricular preponderance and in 3 there was no preponderance. When aortic insufficiency complicated mitral insufficiency, left ventricular preponderance was, of course, more frequent. In more than half, or 4, of the 7 cases of this type there was left ventricular preponderance, and in 3 there was no preponderance.

Duration of the PR Interval—Prolongation of the PR interval is an important sign of active rheumatic carditis, but the seat of the valvular lesion has little bearing on that interval. Accordingly, in our series prolongation of the PR interval was occasionally found in almost all groups, and it mattered little whether an uncomplicated lesion of the mitral valve or a combined lesion was observed at necropsy (chart 1). In only one group was prolongation of the PR interval particularly frequent, the cases of three lesions—mitral, aortic and tricuspid—com-

bined This recalls the fact that prolongation of the PR interval sometimes is the forerunner of auricular fibrillation By the same token, auricular fibrillation also was exceedingly frequent in this same group

Changes in the Q Wave—The initial ventricular deflection (Q wave) was present in lead III in 67 of the 113 cases of mitral valvular disease In only 20 cases did this deflection appear in lead I An analysis of the appearance of the Q wave in the eight different groups of cases of mitral disease (with or without other valvular lesions) did not reveal any significant results A deep Q wave, measuring 25 per cent or more of the height of the R wave, was found in only 6 of the 113 cases In all these 6 cases mitral stenosis was associated with disease of the aortic valve, either stenosis or insufficiency In these cases the voltage of the remainder of the ventricular complex was also relatively high

Changes in the Duration of the Main Ventricular Complex (QRS)—An analysis of this sign (table 1) reveals that mitral valvular disease per se has little influence on intraventricular conduction In only 12 of the 113 cases did the duration of QRS exceed 0.1 second, and all but 3 of these 12 were cases of aortic insufficiency complicating mitral valvular disease It is well known that aortic insufficiency often produces an increase in the duration of QRS Mitral stenosis does not produce such an increase The average duration of QRS was 0.07 second in the cases of pure mitral stenosis, as well as in those of mitral stenosis complicated with aortic stenosis or with tricuspid stenosis, and slightly greater (0.08 second) in cases of mitral stenosis associated with aortic insufficiency and in the larger group of cases of mitral stenosis associated with both aortic and tricuspid valvular disease

Voltage of QRS—Pardee⁵ has stated that many patients with marked mitral stenosis have large excursions of QRS, and he has attributed the increased size of the deflections to cardiac hypertrophy This statement is not borne out by our investigation (table 1) Pardee gave 16 millivolts as the upper limit of normal for the voltage of QRS In not one of our 19 cases of uncomplicated disease of the mitral valve was the QRS complex higher than 16 millivolts, and in only 4 of these 19 cases was the voltage 15 or 16 millivolts The average voltage of QRS in all these 19 cases was 10 millivolts Whether the stenosis was of the "button-hole" type or only moderate did not affect the voltage of QRS at all The voltage of QRS in cases of mitral insufficiency without stenosis was no different from that found in mitral stenosis

The observation of the normal voltage of QRS in mitral stenosis led us to investigate another problem In rheumatic valvular heart disease

5 Pardee, H. E. B. *Clinical Aspects of the Electrocardiogram*, New York, Paul B. Hoeber, Inc., 1928, pp. 50 and 76

does hypertrophy of the right ventricle alone ever result in high voltage of the QRS complex? In congenital heart disease high voltage is not uncommon when the right side of the heart is very large. In 16 of our 19 cases of uncomplicated disease of the mitral valve, there was hypertrophy of the right ventricle, and in 3 of these the right ventricle was huge. Yet, as was mentioned before, in all these cases the voltage of the QRS complex was normal. The average weight of the heart in this group was 445 Gm. In the group of cases of mitral valvular disease with tricuspid stenosis the hearts were of about the same size as those in the first group, and their average weight was 455 Gm, while the voltage of QRS, with 2 minor exceptions, was also within normal limits. Decisive information, however, was obtained from a study of the third group, cases of mitral valvular disease with tricuspid insufficiency. It is commonly known that tricuspid insufficiency leads to extreme enlargement of the heart. This was generally true in our group of 13 cases. The average weight of the heart was 556 Gm, and a large part of this weight was due to hypertrophy of the right ventricle. In spite of this marked right ventricular hypertrophy, in no case of mitral valvular disease with tricuspid insufficiency was there high voltage of QRS in the electrocardiogram. Fifteen millivolts was the highest figure. In marked contrast to this normal voltage were the findings in cases of mitral valvular disease associated with aortic insufficiency. The presence of aortic insufficiency had a marked effect on the voltage of QRS, and the highest excursions, up to 28 millivolts, were found in these cases. Cases in which the left ventricle was very large were of course prevalent in this group.

We are justified in concluding from these findings that of the two ventricles the left is the one which contributes more to the voltage of the ventricular complex and that in rheumatic valvular disease hypertrophy of the right ventricle does not commonly result in high voltage of this complex. These observations are reminiscent of a common fluoroscopic finding. The contractions of the right ventricle, as seen on the fluoroscopic screen, are never as vigorous as those of the left ventricle. The parallelism is obvious, even though it is known that the voltage of the electrocardiogram is no simple function of the strength of the contraction.

Equally illuminating was a separate analysis of 7 cases of mitral stenosis in which an atrophic left ventricle was noted on postmortem examination (table 2). The height of QRS in these 7 cases varied from 5 to 16 millivolts, with an average of 10 millivolts—no lower than that in the rest of the cases in which there was no aortic insufficiency. While the observations on tricuspid insufficiency previously described show the right ventricle to play a minor role in producing the voltage of QRS, these cases of atrophy of the left ventricle demonstrate clearly

that the size of the left ventricle does not alone determine the voltage of the QRS complex and that the rôle of the right ventricle is by no means negligible. It is seen that hypertrophy of the right ventricle alone can produce so considerable a voltage as 16 millivolts.

When analyzing the voltage of QRS, all extraneous factors which might possibly influence it had, of course, to be considered. That such a condition as pleural or pericardial effusion led to the exclusion of a case has already been mentioned. It occurred to us that adhesive pericarditis might have a similar depressing effect on the voltage of the ventricular complex. All cases of chronic adhesive pericarditis therefore were grouped together, regardless of the nature of the existing valvular lesion. Twenty-one of our 113 cases fell into this group. The average voltage of QRS in the cases in this group was 11 millivolts, practically the same as in the remainder of the cases and certainly no lower. In only 3 of these 21 cases was the voltage low

TABLE 2—Data Regarding Eight Cases of Pure Mitral Stenosis (Atrophy of the Left Ventricle)

Case Number	Q Wave		Duration of QRS, Sec	Highest Voltage of QRS, Millivolts	Ventricular Preponderance
	Lead	Millivolts			
1	III	1	0.07	9	Right
2			0.07	3	None
3	III	2	0.08	14	Right
4			0.08	16	Right
5	III	1	0.06	5	None
6	III	1	0.06	9	Right
7	III	2	0.08	6	Right
8	III	1	0.06	9	Right

(below 7 millivolts), and in only 1 case was the voltage high (17 millivolts). Thus we found that chronic adhesive pericarditis had no definite effect on the voltage of QRS.

Changes in the T Wave—Inversion of the T wave has been shown to be a concomitant of ventricular preponderance. Master⁶ showed that inversion of T_3 , or both T_2 and T_3 , is commonly associated with marked enlargement of the right ventricle, whereas inversion of T_1 , or both T_1 and T_2 , is commonly associated with enlargement of the left ventricle. This was confirmed by our investigation. As expected, inversion of T_3 was particularly frequent. In 7 of the 19 cases of uncomplicated disease of the mitral valve this sign was noted. With two exceptions, these were the same cases as those in which the tight "button-hole" type of stenosis of the mitral ostium and marked hypertrophy of the right ventricle were observed post mortem. In the group of cases of uncomplicated disease of the mitral valve there were 3

6 Master, A. M. Right Ventricular Preponderance (Axis Deviation) of the Heart, *Am J M Sc* 186:714, 1935.

cases of extreme enlargement of the right ventricle, and in all 3 inversion of T_3 was noted. Whenever both T_2 and T_3 were found inverted or diphasic, necropsy later showed a very large right ventricle. In cases of mitral and tricuspid valvular disease there was inversion of T_3 , or T_2 and T_3 most frequently, and the largest right ventricles were likewise found in this group. In the cases of mitral valvular disease complicated with aortic insufficiency, on the other hand, inversion of T_1 , with or without inversion of T_2 , was not infrequently found (in 4 of 19 cases), reflecting the marked enlargement of the left ventricle common to that condition. In the large group of cases in which there were three lesions both types of tracings were noted, when aortic insufficiency was the predominant lesion, inversion of T_1 was frequently found, with or without inversion of T_2 . When the tricuspid lesion predominated, however, inversion of T_3 , with or without inversion of T_2 , occurred frequently.

Comparison of Electrocardiograms and Postmortem Observations — Pardee⁵ has stated that the electrocardiogram will suffice in 75 per cent of cases to place the relation of the ventricular weights. To determine how reliable the electrocardiographic signs of ventricular preponderance were in our series, the autopsy records of all 113 cases were examined. In each case it was determined whether the left or the right ventricle predominated in size by noting the degree of hypertrophy as reported in the autopsy record. This anatomic relationship was then compared with the electrocardiographic findings of ventricular preponderance in the same case.

In only 22 of the 107 cases so examined⁷ were there no signs of ventricular preponderance. In the remaining 85 cases there were 45 instances of right ventricular preponderance, 20 of left ventricular preponderance, 12 in which a tendency to right ventricular preponderance was noted and 8 in which a tendency to left ventricular preponderance was noted.

In 76 of these 85 cases (89 per cent) there was agreement between the electrocardiographic and the autopsy observations, in only 9 cases (11 per cent) was there disagreement. In 5 of these 9 cases there was right ventricular preponderance, in 2 left ventricular preponderance, in 1 a tendency to right ventricular preponderance and in 1 a tendency to left ventricular preponderance.

The 22 cases in which the electrocardiogram showed no preponderance were then analyzed. In half of them it was observed that the two ventricles were equally hypertrophic. The electrocardiogram in these cases therefore expressed the anatomic relationship correctly.

⁷ From the total of 113 cases 6 had to be omitted from these correlation studies because preponderance was variable.

But necropsy showed definite preponderance of the left ventricle in 7 and of the right in 4 of the other 11 cases. Here the information given by the electrocardiogram was actually erroneous. A small part of these 11 failures (2 cases) can be explained by inadequacy of the definition of "tendency to right ventricular preponderance." These 2 are the only cases in which a determination of the electrical axis, according to Einthoven's tables,⁸ would have yielded better results and shown preponderance correctly. The remaining 9 failures, however, are unexplained. They force us to the conclusion that electrocardiographic signs of ventricular preponderance are reliable only when present. When the electrocardiogram shows no preponderance, then marked anatomic preponderance of either ventricle may yet exist and may come to light only at necropsy.

COMMENT

Lewis³ has stated "The electrocardiograms of mitral stenosis are often so characteristic that the valve lesion may be diagnosed from these curves alone." What, then, is the typical electrocardiogram of mitral stenosis,⁹ and how often does it appear? Our analysis has attempted to answer this question.

Perhaps the most valuable lesson to be learned from this study is the realization of the importance of the associated valvular lesions. It must not be forgotten that at the bedside an associated tricuspid lesion usually cannot be recognized. Yet it is known that lesions of the mitral valve alone are rarer than combined lesions. In our series of 98 cases of mitral stenosis there were only 19 cases of mitral stenosis with or without mitral insufficiency, but there were 79 cases of combined lesions. Cases of pure mitral stenosis without insufficiency and without lesions of other valves are even rarer (only 8 in our series of 113 cases). In other words, the "typical" case of mitral stenosis is not a pure case of mitral stenosis, and the "typical" electrocardiogram

⁸ Einthoven, W., Fahr, G., and de Waart, A. Ueber die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen, *Arch f d ges Physiol* **110** 275, 1913.

⁹ Samojloff, A., and Steshinsky, M. Ueber die Vorofserhebung des Elektrokardiogramms bei Mitralstenose, *Munchen med Wchnschr* **56** 1942, 1909. Steriopulo, S. Das Elektrokardiogramm bei Herzfehlern, *Ztschr f exper Path u Therap* **7** 467, 1909-1910. White, P. D., and Bock, A. V. Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am J M Sc* **116** 17, 1918. White, Paul D., and Burwell, C. S. The Effect of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, *Arch Int Med* **34** 529 (Oct) 1924. Alexander, A. A., Knight, H. F., and White, Paul D. The Auricular Wave of the Electrocardiogram. Clinical Observations with Especial Reference to Pulmonic and Mitral Stenosis *ibid* **36** 712 (Nov) 1925.

of mitral stenosis, therefore, is the electrocardiogram of a combined lesion, mitral stenosis associated with at least one other valvular lesion, usually of the tricuspid valve. For many years the opinion has prevailed that the combination of a notched P wave and right ventricular preponderance is characteristic of the electrocardiogram of mitral stenosis. The results of our investigation do not bear this out. Notching of the P wave definitely remains the most characteristic electrocardiographic sign of mitral stenosis, and in 14 of the 16 cases of mitral stenosis this sign was present. Right ventricular preponderance, however, was found in less than half the cases in this same group and in only 45 cases in the entire series.

Mitral stenosis with insufficiency may be expected to show a notched, often broad P wave of moderate height and no ventricular preponderance or tendency to right ventricular preponderance (chart 1 *A*). If there is right ventricular preponderance, the stenosis of the mitral ostium is usually very tight (chart 1 *B*). If there is marked right ventricular preponderance and if at the same time the notched P wave is very high and wide, the presence of an associated tricuspid lesion may be safely assumed (chart 2 *A*, *C* and *D*). The occurrence of auricular fibrillation or flutter, while not uncommon in uncomplicated mitral stenosis, also would help to favor the diagnosis of an associated lesion of the tricuspid valve.

On the other hand, left ventricular preponderance absolutely excludes the diagnosis of uncomplicated mitral stenosis, provided hypertension can be ruled out. This statement is of practical importance. A soft protodiastolic murmur at the base of the heart in a case of clearcut mitral stenosis in which left ventricular preponderance is revealed in the electrocardiogram is not a Graham Steel murmur but indicates aortic insufficiency. If there is left ventricular preponderance and high voltage of QRS, with a duration of the main ventricular deflection of 0.1 second, associated with only moderate notching of the P wave (which is not very wide), then the diagnosis of aortic insufficiency and disease of the mitral valve may be assumed (chart 3 *C* and *D*). The presence of right ventricular preponderance does not rule out the possibility that an aortic insufficiency is associated with mitral stenosis. The occurrence of auricular fibrillation would have no weight in the decision for or against aortic insufficiency. As is natural, those cases in which the signs of aortic insufficiency (high pulse pressure, loud diastolic murmur and large left ventricle) are marked are usually also the ones in which left ventricular preponderance, a wide QRS and high voltage are noted. By the same token, the electrocardiogram is sometimes of little help when in a case of clearcut mitral stenosis coexisting insufficiency of the aortic valve is looked for before the clinical examination reveals its obvious signs.

The picture is most varied when the rheumatic process has affected three or all four valves. Here the electrocardiogram is the least characteristic. While right ventricular preponderance is more frequent, left ventricular preponderance or no preponderance may be present. Auricular fibrillation was most frequent in this group, occurring in 14 of 32 cases of our series, besides 1 case of auricular flutter. There is one sign which, though uncommon, when it does occur seems characteristic of the coexistence of three valvular lesions, i e., complete change of ventricular preponderance from that of the right ventricle to that of the left ventricle or vice versa. This reflects the changing interplay of the different lesions and their specific effect on the dynamics of the heart. In a case of combined mitral, aortic and tricuspid lesions the aortic insufficiency may be the principal lesion at one time, and left ventricular preponderance may be shown, while at another time the tricuspid lesion may become more marked, and this change may express itself in a shift to right ventricular preponderance.

The Electrocardiogram of Mitral Insufficiency—On the autopsy table it is often difficult to decide whether there is stenosis alone or stenosis with insufficiency of the mitral valve. In the small series of 8 cases of mitral stenosis in which there was an atrophic left ventricle (table 2) we may be sure there was no mitral insufficiency. Yet, with regard to the P wave, the voltage and the ventricular preponderance, the electrocardiograms in these 8 cases did not in any way differ from those in the remaining cases of mitral stenosis, in which presumably there was also mitral insufficiency. When, on the other hand, mitral insufficiency exists alone, without stenosis, the picture is definitely different.

Mitral insufficiency without stenosis was once thought to be the most common single valvular lesion. At autopsy it is relatively rare. In only 8 of our series of 113 fatal cases of rheumatic disease of the mitral valve was there mitral insufficiency alone. The fact that in 5 of these 8 cases the patient was 6 years of age or younger shows that mitral insufficiency is an early result of the rheumatic process, whereas mitral stenosis appears only later.¹⁰ In several of these cases a typical apical presystolic rumble was present during life, and therefore the diagnosis was mitral stenosis, yet at necropsy only mitral insufficiency was observed. The electrocardiograms were different from those in mitral stenosis. Better knowledge of the electrocardiogram might have served at least to cast doubt on the clinical diagnosis. Several features

¹⁰ It has been shown (Bland E. F., White, P. D., and Jones, T. D. The Development of Mitral Stenosis in Young People, *Am Heart J* 10 995, 1935) that the ultimate development of extensive valvular deformity either with or without actual stenosis probably requires a minimum of two years.

distinguish the electrocardiogram in the cases of mitral insufficiency from that in cases of mitral stenosis in our series (chart 1 *C* and *D*) First of all, auricular fibrillation never occurred in any of our cases of mitral insufficiency, no matter whether that lesion existed alone or was associated with aortic insufficiency Second, the P wave was different A comparison of *A* and *B* with *C* and *D* in chart 1 will illustrate this point In only half the cases of mitral insufficiency was the P wave notched When notching did occur, it was slight, and the P wave rarely was wide The PR interval was usually normal, and the duration of QRS was short, about 0.06 second The voltage of QRS in cases of pure mitral insufficiency was slightly lower than that in mitral stenosis Lastly, right ventricular preponderance never occurred, there was usually no preponderance or tendency to left ventricular preponderance Taken all together, these characteristics distinguish the typical electrocardiogram of a patient with mitral insufficiency from that of a patient with mitral stenosis with a fair degree of accuracy

TABLE 3—*Correlation of Electrocardiographic and Anatomic Observations of Ventricular Preponderance*

	Number of Cases	Agreement	Disagreement
Right ventricular preponderance	45	40	5
Left ventricular preponderance	20	18	2
Tendency to right ventricular preponderance	12	11	1
Tendency to left ventricular preponderance	8	7	1
Total	85	76 (89%)	9 (11%)

Finally, a few words must be said about our attempt to correlate the electrocardiographic signs of ventricular preponderance and the postmortem observations From that correlation one important fact is learned In our series the electrocardiogram was 89 per cent reliable in indicating ventricular preponderance whenever signs of preponderance were present Valvular lesions, as a rule, result in an altered anatomic relationship between the ventricles The effect of this altered anatomic relationship usually far outweighs the extracardiac factors, such as the type of chest and the height of the diaphragm All pathologic processes affecting the electrocardiographic signs of ventricular preponderance, such as a large hydrothorax and diaphragmatic abnormalities, were of course carefully excluded from this series These conditions can in most cases be ruled out by the clinician If they are ruled out and if signs of ventricular preponderance are present, the electrocardiogram expresses anatomic relationship in such a high percentage of cases (89 per cent) that one can rely on it The terms right ventricular preponderance and left ventricular preponderance appear justified by the results of our correlation In the last few years they

have frequently been replaced by the terms left axis deviation and right axis deviation. Yet it must be remembered that an electrical axis of the heart does not actually exist. It is a mathematical abstraction and surely not itself of great practical significance. On the other hand, knowledge of the preponderance of one ventricle over the other may be of great clinical importance. In cases of rheumatic valvular heart disease, therefore, it seems to us, the terms left ventricular preponderance and right ventricular preponderance are more expressive and more practical, and we believe that they should not be replaced by the terms left axis deviation and right axis deviation.

SUMMARY

Reports of 113 fatal cases of rheumatic disease of the mitral valve with autopsy records were collected and the electrocardiograms analyzed. Associated lesions of other valves were found to be the most important single factor affecting the electrocardiograms.

Notching of the P wave was found to be the principal electrocardiographic sign of mitral stenosis. Marked increase in height and width of the P wave, however, was always associated with hypertrophy of *both* auricles and was therefore found to be common only in cases of mitral stenosis associated with disease of the tricuspid valve and in these cases the notching was generally more marked.

Right ventricular preponderance was noted in less than half the cases of uncomplicated disease of the mitral valve and therefore cannot be regarded as a characteristic sign of mitral stenosis. Right ventricular preponderance, however, was generally found in the "button-hole" type of mitral stenosis, but still more frequently right ventricular preponderance was due to an associated lesion of the tricuspid valve.

Left ventricular preponderance was never found in any case of mitral stenosis unless disease of the aortic valve also was present. When mitral stenosis was associated with aortic insufficiency electrocardiographic signs of ventricular preponderance depended solely on the extent of the leak in the aortic valve, in all cases of marked aortic insufficiency with high pulse pressure left ventricular preponderance was present, whether the associated mitral stenosis was slight or marked.

The voltage of the chief ventricular deflection (QRS) in cases of mitral stenosis was never above normal unless aortic insufficiency coexisted. In cases of mitral stenosis with atrophy of the left ventricle, the voltage of QRS was normal.

The electrocardiograms of persons with pure mitral insufficiency without stenosis were distinguished from those of persons with mitral

stenosis by a normal or nearly normal P wave. Auricular fibrillation or auricular flutter never occurred in pure mitral insufficiency, and ventricular preponderance was never to the right.

Complete change from right ventricular preponderance to left ventricular preponderance and vice versa occurred only in cases of mitral stenosis associated with lesions of both the tricuspid and the aortic valve.

A correlation of postmortem observations and electrocardiograms revealed that the electrocardiographic signs of ventricular preponderance, when present, indicated the anatomic relationship of the ventricles correctly in 89 per cent of the cases.

GASTRO-INTESTINAL MANIFESTATIONS OF LYMPHOGRANULOMATOSIS (HODG- KIN'S DISEASE)

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Since the publication of Schlagenhauser's work in 1913, studies of gastro-intestinal lymphogranulomatosis, particularly of the localized type, have been made from the clinical and pathologic points of view, and from these the basis of the present conception regarding this type of Hodgkin's disease has been formed. Cases of Hodgkin's disease of this type warrant particular attention as the formulation of the correct clinical diagnosis is extremely difficult, notwithstanding the numerous laboratory procedures available. The diagnosis is usually made after operation or at necropsy on the basis of the histologic picture and not on that of the gross anatomic features, which cannot be differentiated from those of other pathologic conditions. Two additional cases are here presented, and an analysis is made of the available clinical data regarding seventy-three cases reported in the literature.

In 1889 Pitt described lesions in the stomach and duodenum as part of generalized Hodgkin's disease. Wells and Maver, in 1904, collected reports of a series of two hundred and thirty-eight cases of pseudo-leukemia from the literature. In seven of these the changes were confined principally to the gastro-intestinal tract and consisted of marked hyperplasia of lymphoid tissue. They reported a new case of this specific form and suggested the term pseudoleukaemia gastro-intestinalis. The tendency for the disease to affect the gastro-intestinal tract alone caused them to present the condition "as a subdivision of the general group of cases that presents the anatomical and symptom complex of Hodgkin's disease." Similar cases have been reported by other investigators.¹

Ziegler found that about 35 per cent of the patients with Hodgkin's disease complain of gastro-intestinal disturbances. He attempted a classification of the various types of Hodgkin's disease, including the intestinal type, which he stated is rare. Ewing and later Biggs and Elliott differentiated the conditions noted in the cases reported by Wells and Maver and others from lymphogranulomatosis and placed

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¹ Symmers, Stoerk, Butterfield and Hoffmann

them among those under the heading pseudoleukaemia gastro-intestinalis, which is defined as hyperplasia of the lymphoid tissue in the gastro-intestinal tract

Schlagenhauser, in 1913, described a case of lymphogranulomatosis limited solely to the gastro-intestinal tract, without involvement even of the regional lymph glands. He is credited as being responsible for drawing attention to this type of Hodgkin's disease.

Terplan, Sternberg, Coionini and others have made outstanding contributions to the literature on this subject.

Hayden and Apfelbach have attributed the recent recognition of the localized type of gastro-intestinal lymphogranulomatosis to the following factors: first, the striking similarity in the gross pathologic changes, as evidenced by infiltrations or ulcerations in the gastro-intestinal tract in lymphosarcoma, leukemia, pseudoleukemia and Hodgkin's disease; second, the disappearance of the many designations applied to Hodgkin's disease within recent years. Concomitant with that there has been a better differentiation of the histologic picture associated with lymphogranulomatosis, which has resulted in a more accurate diagnosis of the various lymphomatoses of the gastro-intestinal tract. Terplan has expressed the opinion that before 1913 in many cases of gastro-intestinal lymphogranulomatosis a misdiagnosis of tuberculosis of the bowel or lymphosarcoma was made.

ETIOLOGY

The etiology of Hodgkin's disease is obscure. Stewart and Dobson have enumerated the different etiologic factors as follows: (1) an atypical form of tuberculosis,² (2) a specific infection due to diphtheroid bacillus,³ (3) a neoplastic disease⁴ and (4) a granuloma of unknown etiology. Wallhauser, Simonds and Barron in reviews of the literature on this disease have stated that the majority of the investigators have favored the latter view. Lubarsch classified Hodgkin's disease in an intermediate position between infectious granuloma and a true tumor. Symmers, in 1924, declared that "Hodgkin's disease does not provide any criteria by which it may be grouped either among the inflammatory diseases or among the neoplasms" and said he believed that it is an infection of the hemolytotoxemic system.

GROSS PATHOLOGIC FEATURES

Terplan divided cases of Hodgkin's disease of the gastro-intestinal tract into two groups, namely: (1) cases in which the gastro-intestinal tract is exclusively involved and (2) cases in which the gastro-intestinal lesions are part of a generalized or disseminated disease.

² Sternberg, Fraenkel and Lichtenstein

³ Bunting and Yates

⁴ Klemperer, Mallory, Warthin and Levin

The process is the same for the two types and usually starts as a nodular infiltration in the submucosa, which then protrudes into the lumen or invades the other coats of the gastro-intestinal wall. In the early stages of the disease isolated nodules or small tumors are present only in the submucosa. One can distinguish (1) the ulcerating type of lesion, which is more common and consists of numerous ulcers and infiltrations of the stomach and bowel, and (2) the tumor-like form, which may also be subdivided into (*a*) nodular infiltrations that involve a small segment, varying in size from that of a pinhead to that of a tangerine, and (*b*) a more diffuse involvement, which produces stricture of the bowel and is difficult to differentiate from carcinoma or sarcoma. Cases of the latter type of lesion with intestinal obstruction have been reported.⁵ Intussusception has been noted.⁶ Steindl described a case of pyloric obstruction. Sternberg described another type, which is characterized by diffuse thickening of the wall, with prominent deep sinuous folds of thickened mucosa or rugae, described as resembling the convolutions of the cerebrum.

The ulcer is irregular, with firm, elevated grayish white margins. The base of the ulcer may be clean or covered with a granular exudate. No tubercles can be demonstrated in the floor of the ulcer or serosa. The infiltration progresses from the margin of the ulcer and invades the adjacent tissues. It usually spreads to the regional lymph nodes, and the mesenteric nodes are practically always involved. The mesentery may also be diffusely infiltrated, presenting a tumor-like mass. Any portion of the gastro-intestinal tract may be involved, but the sites of predilection are the stomach, jejunum and ileum. Several parts of the tract are usually involved at the same time. In the stomach the pylorus is the region most frequently infiltrated.

The ulceration in lymphogranulomatosis frequently involves the upper part of the gastro-intestinal tract, in contrast to the lesion in tuberculosis, which involves the lower segments. Schlagenhauser stressed this as an important point in the differential diagnosis between the two conditions.

The ulcerating process may extend through the various coats of the intestinal wall, perforating into the general peritoneal cavity and resulting in peritonitis.⁷ Hemorrhage and severe anemia have been observed.⁸

Although the principal manifestations of the disease are in the gastro-intestinal tract, dissemination to other organs, e. g., the spleen, liver, pancreas or peritoneum, may take place. The spleen and liver

5 Catsaras and Georgantas, de Groot, Oglobina and Heilmann

6 Pamperl, Pissarewa and Hammelmann

7 Warfield and Kristjanson, Novotny, Hayden and Apfelbach, Slovaček, Wald, Coronini, Biebl, Grevillius and Baumgartner

8 Schlagenhauser, Sussig, Hanneborg and Coronini

are rarely enlarged. However, despite the absence of hepatosplenomegaly, in an analysis of seventy-three cases reported in the literature, in fifty of which postmortem examination was made, infiltrations were noted in the liver in eleven and in the spleen in fifteen. The pancreas was involved in six cases and the lungs in four. Lymphogranulomatous involvement of the esophagus, peritoneum, pleura, gallbladder, kidneys, thyroid, bone marrow, ovaries, submaxillary gland, pharynx or heart was observed in several cases. Enlargement of the superficial glands is infrequent.⁹

The coexistence of old and active tuberculosis was noted by some investigators,¹⁰ the cases representing approximately 10 per cent of those reviewed.

Typical Hodgkin's disease usually presents a characteristic histologic structure, on which depends its recognition as a specific disease. It is described as a progressive diffuse granulomatous process which primarily involves lymphadenoid tissue. The initial change is hyperplasia of the lymphoid reticulum, this is followed by the formation of a peculiar granulation tissue containing a wide variety of cells (polymorphocellular tissue), which replaces the normal architecture. This tissue undergoes necrotic changes, and the process terminates with the formation of hyaline fibrous tissue. The chief characteristic of the cytologic picture is the polymorphous appearance of the tissue, giving to it a granulomatous character. The tissue is composed of varying quantities of small and large lymphocytes, reticulum cells, plasma cells, eosinophils, polymorphonuclear neutrophils, fibroblasts and mononuclear and multinuclear giant cells (described by Sternberg and Reed). In some instances there may be variations from the classic picture, which present a complex problem to the pathologist, so that histologic classification may be difficult.

REPORT OF A CASE

CASE 1—S. G., a 63 year old nurse, was admitted to the medical service of the Mount Sinai Hospital on Sept. 17, 1929. She was well until several weeks prior to entry, when she complained of epigastric distress and heaviness after meals, with occasional nausea and vomiting, accompanied with constipation.

Past History—Appendectomy was performed in 1916 and panhysterectomy for carcinoma of the uterus in 1927.

Physical Examination—The pupils were equal and regular and reacted to light and in accommodation. Hearing was unimpaired on both sides. Both drums were normal. The breathing was unobstructed, and no abnormality was noted in the nose, mouth or throat. The trachea was in the midline and freely movable. No masses were palpable. There was no evidence of adenopathy. The chest was symmetrical and moved freely with respiration. The percussion note was resonant.

⁹ Reimann, Scott and Forman, Coronini and Tschilow.

¹⁰ Heimann-Hatry, Terplan and Wallesch, Schlagenhauser, Kaznelson, Kan, Sussig, Bonciu and Hayden and Apfelbach.

Tactile and vocal fremitus were equal on the two sides. Breathing was vesicular. No râles were audible. The heart was not enlarged on percussion. The sounds were regular as to rate and rhythm. No murmurs were heard. The abdomen was soft and symmetrical. There were two vertical scars in the lower portion of the abdomen, one in the midline and one to the right of the midline (results of former operations). No tenderness or rigidity was noted. The liver and spleen were not palpable. Neurologic examination revealed no abnormality. Rectal examination showed no evidence of disease.

Laboratory Examination—A Rehfuess test meal showed achlorhydria, with a total acidity of 19.

Examination of the blood showed hemoglobin, 63 per cent, red blood cells, 4,030,000, white blood cells, 10,200, polymorphonuclears, 81 per cent, eosinophils, 2 per cent, monocytes, 12 per cent, lymphocytes, 3 per cent, and myeloblasts, 2 per cent.

Examination of the urine revealed no abnormality.

Gastro-intestinal examination revealed a defect involving the antrum and part of the body of the stomach. The duodenal bulb appeared regular. There was a slight delay in gastric motility. A diagnosis of a prepyloric new growth was made.

Course—After a two week stay in the hospital the patient was much relieved symptomatically. Roentgen therapy was instituted. She was discharged on September 30 and went home to recuperate from her illness. In the middle of December pain began to develop in the spine, with vague, generalized muscular pains and stiffness. The pain in the spine rapidly became worse, so that the patient could hardly bend. There was exquisite tenderness over the lumbar portion of the spine. She returned to New York, and several days before her readmission to the hospital new pains developed on the adductor side of the left thigh and in the left popliteal region, in addition to the pain and tenderness in the back. The patient had had no symptoms referable to the gastro-intestinal system since discharge from the hospital. She complained of weakness. There was no loss of weight. On December 28 she was readmitted to the hospital.

Physical Examination—The pupils were equal and regular and reacted actively to light and in accommodation. The ears, nose and throat were normal. The lymphatic system showed no glandular enlargement. The chest moved freely on respiration. There was no impairment of resonance. The breathing was vesicular. No râles were heard. The heart was not enlarged, and the sounds were regular in rate, rhythm and volume. The aortic second sound was louder than the pulmonic second sound. The abdomen was soft. No masses were palpable. There was slight tenderness in the left upper quadrant of the abdomen. The liver and spleen were not enlarged. Tenderness on pressure was elicited over both sacro-iliac joints, especially on the right. The motion of the thighs was not limited or painful. Over the lateral aspect of the right fibula below the knee was a painless fixed hard red swelling.

Laboratory Examination—The blood count showed hemoglobin, 66 per cent, red blood cells, 3,770,000, white blood cells, 11,800, polymorphonuclears, 74 per cent, lymphocytes, 21 per cent, monocytes, 3 per cent, and eosinophils, 3 per cent.

Roentgen examination of the lumbosacral portion of the spine showed a moderate degree of spondylitis and arthritis of both sacro-iliac synchondroses and hip joints. Examination of the legs, including the knees and ankles, showed a fairly marked degree of hypertrophic arthritis of the knees.

Gastro-intestinal examination showed the filling defect as previously reported. The process appeared to be further advanced, with more invasion of the lumen.



Fig 1 (case 1) —Roentgenogram of the stomach made at the time of the patient's admission to the hospital, showing the filling defect involving the antrum and part of the body

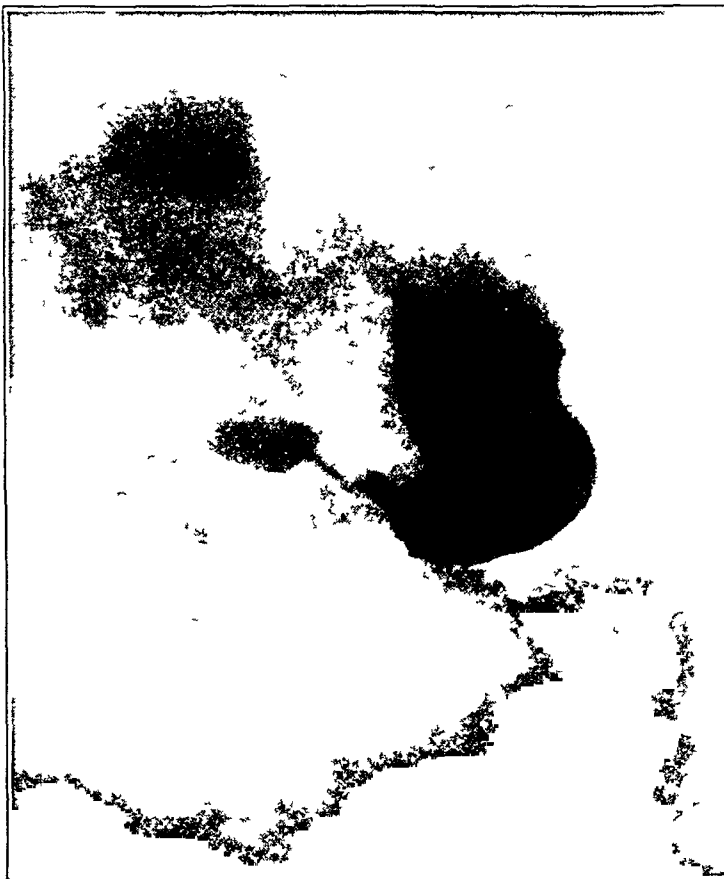


Fig 2 (case 1) —Roentgenogram made when the patient was readmitted three months later. The filling defect has increased, with apparently more invasion of the lumen of the stomach in the region of the antrum and part of the body. The lumen of the stomach presents as a narrow channel in the prepyloric region.

of the stomach in the region of the antrum and part of the body. The lumen of the stomach presented as a narrow channel in the prepyloric region. Six hours after the meal a minute residue was present in the stomach. The duodenal bulb was small and complete.

Operation—The patient was given a transfusion of blood on Jan 22, 1930, and an operation was performed by Dr A. A. Berg. A mass was noted in the posterior wall of the stomach. Partial gastrectomy with no loop posterior suture gastro-enterostomy was performed.

Biopsy—The specimen studied consisted of the resected portion of the stomach and 2 cm of the duodenum. It measured 8 cm on the lesser curvature and 11 cm on the greater curvature. Just off the lesser curvature, on the posterior wall near the region of the pylorus, there was felt a large, indurated resilient lesion surrounded by thickening of the wall. The serosal surface of the greater curvature was studded with small millet-seed-like bodies. There were no glands on the greater or the lesser omentum. The opened stomach revealed an irregular ulcer in the lesser curvature and on most of the posterior wall, which was stellate, with an elevated border and a sloughing base. The ulcer in its greatest length measured 2.5 cm and in its greater breadth 1.5 cm. The surrounding mucosa for a considerable extent gave the impression of having an undetermined sub-mucosal involvement. The resected border seemed to be at least 2 cm beyond the infiltrated area.

The pathologic diagnosis was large round cell sarcoma.

Course—The patient made an uneventful recovery from the operation but gradually started to fail. In April vomiting began, and she had marked anorexia and suffered from pain in the left lower quadrant of the abdomen. An enlarged node in the left axilla was noted at this time. The swelling observed previously over the right fibula had disappeared. Despite supportive treatment the patient continued to fail and died on June 14.

Gross Postmortem Observations—Gastro-Intestinal Tract. The esophagus was normal. The remaining upper third of the stomach was dilated, and the gastro-jejunal opening was patent. There were no ulcerations, but the wall of the stomach was indurated and firm, especially in the rugae, which stood up prominently. The induration extended radially from the gastrojejunal opening onto the anterior and posterior surfaces of the stomach, straddling the lesser curvature. The induration lessened toward the cardia. The jejunum at the point of anastomosis also was indurated, but to a lesser extent. The perigastric fat and lymph nodes were infiltrated by pearly white tissue, which was firm and from which no fluid could be expressed. The infiltrating tissue extended along the chain of lymph nodes on the superior and anterior surfaces of the body of the pancreas to the head but not quite to the tail. The duodenum was normal. The duodenal stump was closed and buried in adhesions. The ileum, colon and rectum were normal.

Uterus and Adnexa. The uterus and adnexa were not present. The cervix could not be found. The space between the rectum and the bladder was obliterated by adhesions.

Liver. The liver was normal in size and shape but somewhat firmer than normal. On section the central lobular areas were congested. The rest of the liver appeared somewhat fatty. A few scattered nodules the size of a pea were noted in the left lobe of the liver. They were round, pearly white, firm and distinctly demarcated from the rest of the hepatic tissue. In one area a surface nodule on the edge of the liver was contiguous with the infiltration in the gastro-hepatic omentum.

Pancreas The pancreas appeared normal The peripancreatic nodes were involved by tumor tissue

Other Organs The lungs, heart, spleen, kidneys, bladder, ureters and adrenal glands showed no gross pathologic changes

Microscopic Postmortem Observations—**Stomach** Infiltration by tumor tissue into the jejunum was noted across the line of anastomosis There was a distinct change toward a more polymorphous cellular infiltration, with many giant cells, plasma cells, lymphocytes and eosinophilic polymorphonuclears, resembling a Hodgkin granuloma The infiltration extended into the muscularis Many cells with hyaline degeneration and a signet ring appearance were seen

Liver Edema and congestion were noted, with granular degeneration and large fatty vacuolation of the hepatic cells Many small infiltrations had destroyed the hepatic structure, producing a picture resembling that of Hodgkin's granuloma

Lymph Nodes The structure of the lymph nodes was destroyed and replaced by Hodgkin's lymphogranuloma There were areas of necrosis and fibrosis

Heart The heart showed degeneration of the muscle fibers A few scattered areas of fibrosis were present

Lungs Some foci of bronchopneumonia alternating with areas of emphysema and edema were noted

Kidneys The kidneys showed evidence of degeneration

Other Organs The spleen, pancreas, small and large intestines, adrenal glands, bladder and ureters were normal

Comment—The typical picture of Hodgkin's lymphogranuloma of the stomach, perigastric lymph nodes and liver noted post mortem necessitated a review of the original surgical specimen The infiltration in this specimen was strictly limited to the submucosa and did not invade the muscularis The infiltration consisted of large mononuclear cells, each with a conspicuous large pale nucleus and a sharply outlined red nucleolus, small dark nucleated cells (resembling lymphocytes) of various sizes and many polymorphonuclear cells, among which were many eosinophils, and abundant mitotic figures At the edges of the infiltration was noted arrangement of these cells in smaller and larger nodules Occasional multinucleated cells with darker stained nuclei were seen

A consideration of the following factors would have permitted a diagnosis of Hodgkin's disease rather than round cell sarcoma from the specimen removed for biopsy four months before (1) the limitation of the infiltrated cells in the submucosa and (2) the polymorphism of the cell types

Diagnosis—The diagnosis was lymphogranulomatosis of the stomach, with infiltration of the gastrohepatic omentum, the perigastric and peripancreatic lymph nodes and the liver The status was typical of that following partial gastrectomy, with degeneration of the heart, liver and kidneys, and of that following panhysterectomy for carcinoma of the uterus and appendectomy

COMMENT

Steindl, in 1924, reported the first case of lymphogranuloma localized to the stomach in which operation was successful The clinical diagnosis was carcinoma of the stomach Operation revealed an infiltrating tumor of the pyloric and prepyloric regions, with involvement of the glands in the lesser curvature and gastrocolic omentum No evi-

dence of lymphogranulomatosis was noted in the other abdominal organs. Gastric resection was performed. The patient was well one year after operation.

Reports of the following cases have been obtained from the literature.

1 Similar cases in which operation was successful ¹¹

2 Isolated lymphogranulomatous lesions of the stomach, established by postmortem examination ¹². Singer stated that extreme caution must be exercised in deciding that gastro-intestinal lymphogranulomatosis is strictly isolated. The fallacy of surgical procedure must be appreciated, as the surgeon may overlook lesions in organs that are inaccessible or lesions that are minute. One of Vasilu's patients died shortly after gastric resection. Autopsy revealed a small infiltration in the spleen. In this case operation had disclosed only a mass in the stomach, with no evidence of disease elsewhere. The postmortem examination showed small infiltrations in the liver.

3 Cases of lymphogranulomatosis of the stomach with abdominal involvement ¹³

4 The presence of coincident and limited involvement of the stomach and bowel ¹⁴

REPORT OF A CASE

CASE 2—I S., a 36 year old woman, was admitted to the medical service of the Mount Sinai Hospital on Dec 27, 1934. She was well until one year before entry, when she complained of pain in the umbilical region which came on from one-half to two hours after meals and was associated with nausea. The pain was pressing and did not radiate. It was relieved by induced vomiting but not by food or alkali.

Past History—Ten months before admission to the hospital the patient was prescribed a Sippy diet and rest in bed, which relieved the pain. At this time she was sent to another hospital, where she remained for three weeks, with the continuation of the Sippy diet and rest. A gastro-intestinal examination revealed no abnormality. Two weeks after discharge from the hospital she began to experience epigastric pain that was unrelated to meals and was initiated by nervousness and anger. The pain was burning in character and unrelieved by the Sippy diet.

Four months before admission to the Mount Sinai Hospital she entered another hospital, where complete examination of the gastro-intestinal tract failed to reveal any abnormality. She was given a blood transfusion and placed on a rich diet, which seemed to increase her appetite and relieve the epigastric pain. During

11 Neuber, von Redwitz, Thiemer, Froboese and Vasilu

12 Kan, Singer, Mittelbach, Baumgartner, Dudits and Sussig

13 Hayden and Apfelbach, Hess, Terplan, Scott and Forman, Tschilow, Dudits and Coronini

14 Coronini, Drope, de Groot, Terplan and Wallesch, Novotny, Kaznelson and Schlagenhauser

her stay in the hospital pain developed in the left lower quadrant of the abdomen, coming on two or three hours after meals and being associated with abdominal distention and inability to pass gas or feces. She received daily enemas and colonic irrigations, which relieved the distention.

On admission to the Mount Sinai Hospital her chief complaints were the epigastric pain associated with nervousness and the colicky pain in the left lower quadrant of the abdomen. She stated that she had never noticed tarry or bloody stools, diarrhea or bouts of fever. During the past year she had become progressively weaker and had lost 23 pounds (10.5 Kg).

For two years she experienced dyspnea and palpitation after climbing two flights of stairs, but for three or four months prior to the present admission to the hospital she had these symptoms even while at rest. No pain in the chest, cough or edema was noted. The patient claimed that she had not observed any tremors or enlargement of the neck.

The menses were regular until nine months before the patient entered the hospital. Since then there had been two periods, the last one occurring six months before entry. Each of these periods lasted for three days, in contrast to the usual duration of five or six days. She denied the possibility of pregnancy.

Bilateral mastoidectomy was performed twenty-six years before the present admission to the hospital.

Physical Examination—The patient appeared pale and emaciated. Scars of the previous bilateral mastoidectomy were noted, with an open sinus, 4 mm wide, on the right side. The right ear drum showed no landmarks, and the membrane was opaque and gray. The left ear drum showed a light reflex but was distorted. There was no discharge. Examination of the chest revealed no abnormality. The breasts were atrophied. A papillomatous wartlike growth was noted in the right nipple. The heart was not enlarged. The first sound was loud and snapping. It was preceded by a faint presystolic rumble, which was brought out best with exercise and with the patient in the left lateral recumbent position. The pulmonic second sound was louder than the aortic second sound. The rhythm was regular. The blood pressure was 88 systolic and 58 diastolic. There was definite clubbing of the fingers. The abdomen was uniformly distended. There was generalized tenderness, which was maximal in the epigastrium and on the left side of the abdomen. There was voluntary spasm in the upper portion of the abdomen and along the entire left rectus muscle. No masses were palpable. There was no evidence of ascites. The liver and spleen were not palpable.

Diagnosis—The diagnosis made by the house physician at the time of the patient's entry was (1) chronic cardiovascular disease with mitral stenosis and (2) tuberculous peritonitis.

Laboratory Examination—The blood count showed hemoglobin, 43 per cent, red blood cells, 2,610,000, white blood cells, 6,100, polymorphonuclears, 84 per cent, lymphocytes, 8 per cent, monocytes, 5 per cent, and eosinophils, 3 per cent. The sedimentation time was thirteen minutes. Chemical analysis of the blood showed amylase, less than 1 mg, calcium, 8.3 mg per hundred cubic centimeters, phosphorus, 4.2 mg, and total proteins, 4.8 mg. The icteric index was 4.

The urine was normal. Analysis of the gastric contents after a Rehfuess test meal showed total acidity 52 and free acid 30. The Wassermann reaction was negative.

The stool showed a positive reaction to guaiac. Examination after the addition of antiformin showed no tubercle bacilli. Sigmoidoscopy showed some tiny pitted

areas suggestive of healed ulcers. Specimens from these ulcers taken for biopsy showed no significant change.

The Mantoux test showed a positive reaction.

Fluoroscopy of the heart revealed prominence of the pulmonary conus but no definite enlargement.

Gynecologic examination disclosed no abnormality.

A gastro-intestinal study on Jan 2, 1935, revealed no abnormality of the stomach and duodenal bulb. Examination of the small bowel two, four, six and eight hours after eating showed the outline to be irregular. There were irregular dilatations and constrictions which were not constant as to location. Reexamination was advised. On January 9 reexamination of the gastro-intestinal tract with special reference to the small bowel again showed evidence of irregular constrictions and dilatations of the small bowel, with delayed motility. At least two of these constrictions were constantly demonstrated. The roentgen findings suggested the possibility of tuberculous peritonitis or of a malignant growth. A barium sulfate enema showed marked irregular spasms in the cecum, the ascending colon and the proximal portion of the transverse colon.

Roentgenograms of the chest on several occasions revealed no abnormality. While in the hospital the patient had sudden attacks of tachycardia, the electrocardiogram showed evidence of supraventricular tachycardia.

Abdominal puncture was performed, a small amount of fluid was obtained, which revealed an occasional polymorphonuclear or mononuclear cell but no tubercle bacilli.

At this time it was decided that exploratory laparotomy was indicated, to be preceded by another gastro-intestinal examination. Meanwhile the patient continued to fail in spite of a high caloric diet and vitamin and liver therapy. Edema of the legs appeared, and the total protein content of the blood continued to be low.

The third gastro-intestinal examination showed the stomach and duodenum to be normal. Observations were made two, four, six, eight and ten hours after eating, in order to study the small intestine. On all the films the distal portion of the jejunum and perhaps the beginning portion of the ileum showed areas of constriction and dilatation. The margins of this portion of the bowel appeared irregular and fuzzy. At the ten hour examination delayed motility of the small bowel was noted. The findings were considered as those seen in nonspecific ulcerating enteritis.

Course—Shortly thereafter profuse diaphoresis developed, and the patient went into a stupor. The hemoglobin value was 40 per cent at this time. A transfusion of 500 cc of citrated blood was given, and the patient responded somewhat. However, she went into a stupor again, and catatonic phenomena developed. This was felt to be due to a toxic exhaustive state. She continued to be in a stupor and there were signs of fluid at the base of the left lung, with marked edema of the ankles, legs and conjunctivae. Despite all supportive treatment the patient died on February 24. During her stay in the hospital the temperature was elevated.

Gross Postmortem Examination—Abdomen. The abdomen was moderately distended. The anterior wall was markedly edematous. The peritoneum was smooth and glistening. The greater omentum was adherent to a proximal jejunal loop. In the pelvis there were several hundred cubic centimeters of free colorless, somewhat turbid fluid, smears of which showed occasional lymphocytes. At the root of the mesentery a firm mass could be felt, which was irregularly outlined and measured 4 by 7 cm in diameter.

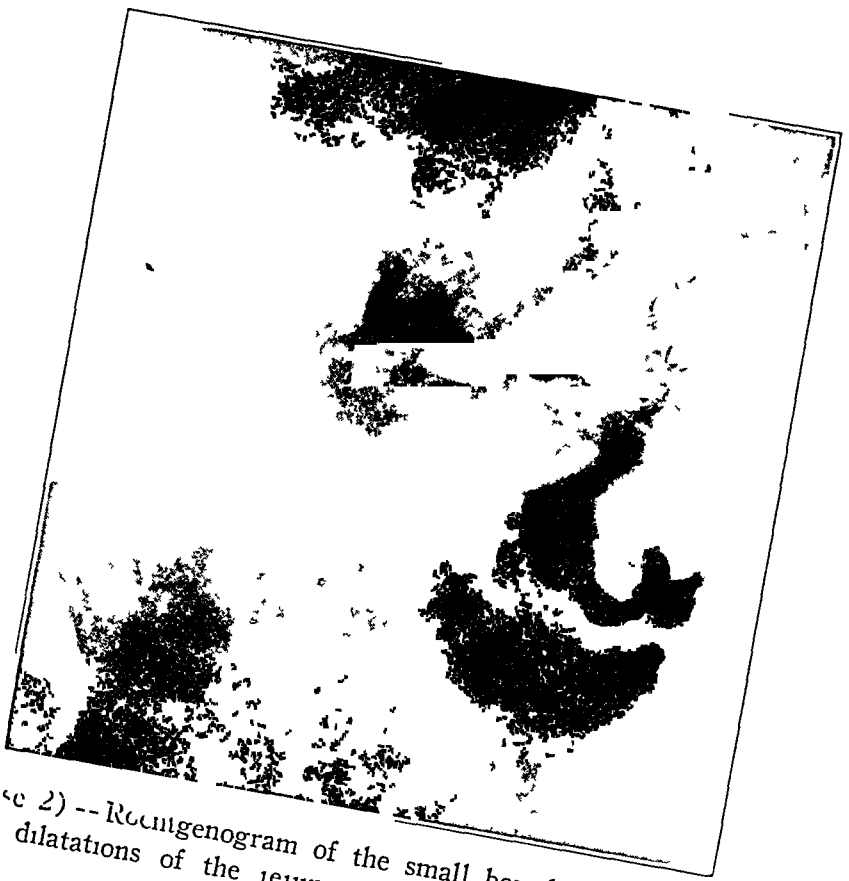


Fig 3 (case 2) -- Roentgenogram of the small bowel, showing irregular constrictions and dilatations of the jejunum. There was delayed motility of the small bowel.

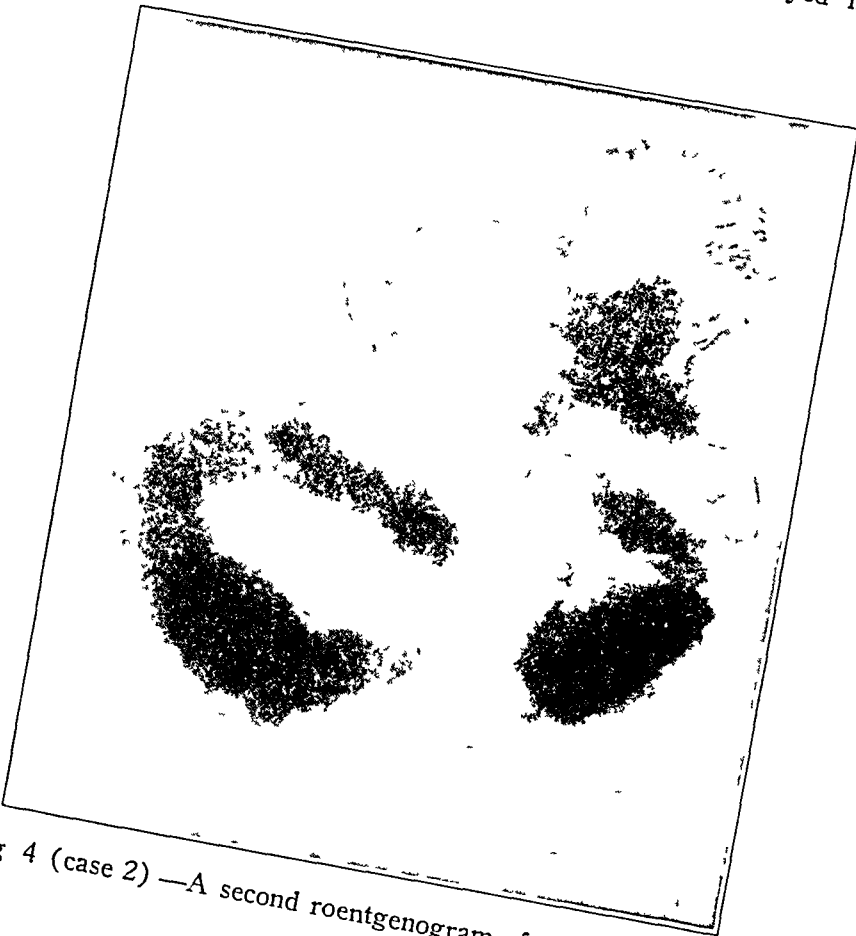


Fig 4 (case 2) -- A second roentgenogram of the small bowel.

Chest In the right pleural cavity there was a moderate amount of clear amber fluid. The left pleural cavity contained a moderate amount of whitish, turbid fluid, smears of which showed many polymorphonuclear leukocytes, no bacteria were seen. There were diffuse rather loose fibrous adhesions over the apex of the right lung posteriorly.

Heart The heart weighed 225 Gm. The pericardial sac contained a moderately increased amount of clear amber fluid. The parietal pericardium showed firm fibrous adhesions to the epicardium along the anterior interventricular groove and over the apex anteriorly. The myocardium was firm and red. The right auricle showed no change. The tricuspid valve was diffusely and moderately opaque and thickened, the anterior and septal leaflets were fused for a distance of about 1 cm. Along the closure line a narrow row of fine translucent and somewhat firm verrucae could be seen. In the right ventricle the trabeculae carneae were slightly prominent and flattened. The left auricle was moderately widened and showed a moderate diffuse opaque thickening of the endocardium, the auricular wall was definitely thickened. The mitral valve presented marked diffuse thickening and was opaque. The leaflets were rigid. A shelf was formed by the rolling of the free edge beneath which the chordae tendineae inserted. These were moderately to markedly thickened and shortened and were fused, especially near their insertions into the valve. Along the line of closure the mitral valve presented a row of slightly firm translucent verrucous excrescences, which measured up to 0.5 mm in diameter. The left ventricle was slightly dilated and hypertrophied, and the apex was rounded. The aortic leaflets presented slight granulation of the surface on the ventricular aspect in the area between the closure line and the free edge. The coronary arteries were patent throughout and showed slight yellow intimal flecking. The orifice of the right coronary artery was narrow. The aorta was elastic and showed little yellow intimal flecking in the abdominal portion.

Lungs The lungs weighed 820 Gm. Except for the apex of the right lung posteriorly, the surface was smooth, glistening and gray, with a tinge of purple. The lungs were subcrepitant throughout. A moderate amount of clear, somewhat frothy fluid flowed on pressure. In the lower lobe of the left lung posterosuperiorly a calcified nodule, 2 mm in diameter, was present. The bronchi showed no changes. The main pulmonary trunk was occluded by a moderately soft dark red blood clot, which continued into the larger and medium-sized branches. The pulmonary veins showed no changes.

Thyroid There was a cyst, 0.5 cm in diameter, in the lower pole of the left lobe.

Adrenals The adrenal glands showed no changes grossly.

Spleen The spleen weighed 75 Gm. The capsule was smooth. The cut surface was firm, flat and moist. The pulp was red, the lymphatic follicles and trabecular tissue could be recognized. An accessory spleen, 1.2 cm in diameter, was present in the gastrosplenic ligament and showed the same structure.

Liver The liver was large, weighing 1,490 Gm. The surface was smooth, and the consistency was somewhat flabby. On section the surface was brownish yellow. Irregularly scattered throughout the liver were many moderately defined yellow areas from 1 to 3 mm in diameter.

Pancreas The pancreas was firm and yellowish gray and presented a normal lobular structure. Around the pancreas and the portal area several moderately firm lymph nodes were present, measuring up to 1.5 cm in diameter. On section they showed a moist homogeneous reddish gray surface.

Gastro-Intestinal Tract The esophagus showed no changes. The stomach was markedly distended and contained several hundred cubic centimeters of

greenish gray turbid fluid In the wall of the stomach a firm nodule the size of a pinhead could be felt The gastric mucosa was covered with thick grayish mucous material The duodenal mucosa was bile stained The duodenum and the upper portion of the jejunum were not distended About 30 cm below the ligament of Treitz the jejunum showed normal brownish gray mucosal folds and had a circumference of about 8.5 cm One of these folds was prominent and firm and could not be lifted up from the intestinal wall On section this fold contained a homogeneous grayish white, firm infiltration, which grossly could not be distinguished or separated from the serosal membrane The infiltrated fold was followed by an area, about 2 cm long, of poorly defined firm, flat elevations, from 0.5 to 1 cm in diameter, and presented a greenish discoloration Beyond this area the jejunal wall was moderately and diffusely thickened throughout and in addition presented firm elevated areas, which sometimes could be recognized as distended and infiltrated mucosal folds and which in some instances showed small firm papillomatous excrescences At this site the serosal membrane was reddish blue, with distinct vascular injection Small firm whitish nodules, apparently subserosal, from 1 to 3 mm in diameter, were prominent at the serosal aspect The greater omentum was adherent to this area The omental adhesions contained a firm lymph node, 1 by 0.5 cm in diameter, which on section presented an irregular and intensely congested periphery, the center being formed by a firm homogeneous white nodule with flat cut surface, it was sharply defined from the congested area, except in one small zone In the distal part of these regions the distentions of the mucosal folds were thin and narrow, they stood about 2 or 3 mm apart from each other The mucosal surface was slightly granular In this area the serosa showed no obvious changes The adjacent area, which was about 3 cm long, showed the intestinal wall to be thinned and bulging, especially in one area, which was 2 cm long and 3 cm wide, and presented an ulcerated mucosal surface with serpiginous elevated edges The base of this zone showed flattened and widened intestinal folds with a reddish gray dull granular mucosa, which presented small shallow oval erosions with a firm gray base or larger and deeper ulcers, which included the muscular layer and had a firm raised serpiginous border and an irregularly infiltrated base

Distally the intestinal wall became gradually thicker and firmer The ulcerations became deeper, their edges steeper and the nonulcerated surface more and more even This zone was 3 cm long and gradually led to an area of marked narrowing of the lumen, which showed a length of 2 cm, its isthmus showing a circumference of 3 cm At this site the wall was 3 mm thick and on cross-section showed a homogeneous grayish white surface The mucosal surface in this vicinity was practically flat and showed slight granulation in some areas Distally, in a zone 4 cm long, the intestinal wall again was thinned and bulged outwardly After 2 cm it regained a lumen of normal width, which again, toward the end of this zone, ran out into a narrowed portion of the jejunum, 3.5 cm in diameter, containing deep punched-out ulcerations with a steep edge and a flat base There were also areas where the intestinal wall was thickened and showed superficial and irregular ulcerations as well as broad flat folds After 4 cm of firm, moderately distended, rather regular intestinal folds, the lumen gradually reached a normal width, with a grossly normal mucosal membrane for a length of 7 cm, while the serosa in the former areas showed the same changes as described for the site of the omental adhesions Here the serosa for the first time showed no gross change Then again an area of diffuse infiltration, with elevation and distention of the folds, was encountered, which was 5 cm long and led to a stricture that was

3.5 cm wide and 1.5 cm long. Beyond this stricture, which gave the same picture as that previously mentioned, the lumen and intestinal wall regained a normal appearance.

At the root of the mesentery was an area measuring about 4 by 7 cm. The lymph nodes measured up to 1.5 by 2 cm. They were firm, and their capsules were fused. The larger part of the cut surface of the nodes showed a moderately firm flat, homogeneously white area, which in most instances was sharply defined. The remainder of the cut surface of these lymph nodes was grayish red, with small irregular red spots. Other lymph nodes, which were somewhat firmer, showed a slightly bulging gray and slightly congested cut surface, with little irregularity and indistinctly outlined white areas 1 by 2 mm in diameter.

Genito-Urinary Tract The kidneys were of equal size and together weighed 22 Gm. The surfaces were congested and smooth, except for several irregular shallow linear markedly congested depressions, which were present especially at the convexity of the kidney. The capsules stripped easily. The cut surface was markedly congested and showed distinct corticomedullary demarcation. The pelves, ureters and bladder showed no changes.

The uterus, fallopian tubes and ovaries showed no changes grossly.

Brain The calvarium was normal. The dura was normal and stripped easily. The meninges were thin and transparent throughout. The sulci, particularly in both frontal lobes, were widened and deepened, and there was moderate convolitional atrophy over the frontal lobes. There was slight congestion of the vessels over the convexity.

Macroscopic Postmortem Examination—**Brain** There were degenerative changes in many nerve cells and some distortion of the cortical lamellations. Small foci of rarefaction and softening were seen. There was a glial reaction in the form of subcortical gliosis. Many vessels possessed thickened walls and showed proliferation of the endothelium.

Jejunum (a) On the edge proximal to the lesion the mucosal membrane showed moderate plasma cell and lymphocytic infiltration, with occasional polymorphonuclear leukocytes. There was slight capillary congestion. The submucosal and muscular layers showed no change. Suddenly the submucosal and muscular layers were seen to be infiltrated, and their structure was obliterated by granulation tissue. Shortly afterward the mucosal membrane became involved. At the site of the first infiltrated intestinal fold the entire wall, except for the serosa and subserosa, was involved, only single islands of mucosal epithelium, fragments of muscular fibers and single muscular nuclei could be recognized. The infiltration consisted of lymphocytes and cells with long oval or rod-shaped nuclei containing finely dispersed granular chromatin and surrounded with slightly eosinophilic homogeneous protoplasm (histiocytes), plasma cells were present.

There were seen numerous scattered polynucleated and mononucleated giant cells with central, polymorphous and overlapping nuclei and sparse basophilic protoplasm. At one point the mucosa was denuded. The surface was covered by amorphous blue-staining material beneath which were many pyknotic nuclei and a narrow zone of leukocytic infiltration. Beyond the first infiltrated fold the intestinal wall became much thinner, and its structure could not be recognized. The external part of the wall consisted largely of collagenous tissue, which was well vascularized and contained long, thin, spindle-shaped cells, round cells and reticulum cells. There were occasional polymorphonuclear leukocytes and plasma cells.

(b) Section through the wall of the first strictured area showed the muscular layer to be well preserved. Only in some areas did the cellular granulation tissue

dip between the muscular bundles of the circular layer. The submucosal layer was infiltrated by granulation tissue, there were large areas of necrosis, which tended to become surrounded by collagenous fibers. The muscularis mucosa, though infiltrated and interrupted in places, could be recognized. In the mucosal area mucosal cells could not be made out, there was capillary granulation, which showed slight compression of the surface. In the adjacent ulcerative area the mucosal, submucosal and circular muscular layers were wanting. The base of the ulceration was formed by a somewhat hyalinized and vacuolated muscular tissue which contained pyknotic nuclei. The remainder of the thin wall was formed by cellular granulation tissue.

(c) Section through the thin area showed stretched-out intestinal mucosa with a moderate diffuse infiltration of lymphocytes, eosinophilic leukocytes and plasma cells.

Section through the first nodular area showed the entire wall involved by the granulation tissue, there were large necrotic areas in which giant cells were obvious. In places the granulation tissue was continuous with the adherent greater omentum.

Section through the area of adherent and normal folds distal to the second stricture showed that in the adherent folds the mucosal and submucosal areas were involved to a moderate degree. The muscularis mucosa and in places the mucosal crypts could be recognized. In certain areas the granulation tissue was continuous with the interstitium of the circular muscular layer. In places the muscular bundles of the longitudinal muscular layers were separated by narrow strands of granulation tissue. The peritoneum showed moderate fibrotic thickening. The adjacent area presented normal jejunal folds the mucosal membrane of which showed diffuse lymphocytic and plasma cell infiltration and several eosinophilic leukocytes.

Lymph Nodes In the lymph nodes of the mesenteric root the lymphatic structure was obscured. The nodes showed granulation tissue with wide areas of caseation. The entire lymph node of the adherent greater omentum was involved, showing a large central area of caseation. No capsule could be made out. The peritoneal fat tissue showed interstitial round cell infiltration and infiltration with granulation tissue. In the portal lymph nodes the sinuses were wide and filled with polymorphonuclear leukocytes. One lymph node showed much fat tissue and congestion.

Cardiovascular System The auricular endocardium showed diffuse fibro-elastic thickening. The mitral valve showed irregular fibrous thickening. This fibrous tissue as well as the auricular subendocardium contained blood vessels. The valve contained many fibroblasts and fibrocytes, which were increased in areas, in some places there were a few lymphocytes.

The ventricular endocardium showed no change. There was slight ventricular interstitial focal fibrosis. The tricuspid valve showed diffuse fibrosis. There were several capillaries in the valve. The aortic valve also showed moderate fibrous thickening.

Lungs The pleura of the upper lobe of the left lung showed no changes. There was diffuse congestion, and a large number of polymorphonuclear leukocytes were present in the alveolar walls throughout the section. The lower lobe of the left lung showed emphysema, congestion and edema. The pulmonary arteries were filled with blood clot, in places their walls showed slight polymorphonuclear and round cell infiltration. In a few small areas the alveoli were filled with polymorphonuclear leukocytes.

Adrenal Glands The adrenal glands showed no change.

Spleen The pulp was irregularly congested and contained many polymorphonuclear leukocytes and a moderate number of round cells

Liver The portal fields showed slight round cell infiltration. The hepatic cells were indistinctly outlined and small, and the protoplasm was cloudy and granular. The cells contained large droplets of fat.

Stomach Section through the small intramural nodule showed a myoma at the edge of the submucosal and muscular layer.

Kidney The capsule was thin, and the surface showed shallow depressions. There was diffuse moderate congestion, more marked in the medulla.

Urinary Bladder There was slight diffuse infiltration in the submucosa by round and polymorphonuclear cells.

Ovaries Section of the ovaries showed no change.

Comment—The diagnoses entertained both clinically and roentgenologically rested between tuberculous peritonitis, lymphosarcoma and nonspecific granulomatous enteritis. Even after all diagnostic aids had been exhausted and carefully studied a definite diagnosis could not be formulated. It was therefore felt that exploratory laparotomy was strongly indicated from the diagnostic and therapeutic standpoints. However, the patient's condition became rapidly worse, and death ensued shortly.

Diagnosis—The diagnosis was as follows: granuloma of the jejunum (Hodgkin's) with caseating mesenteric lymph nodes, rheumatic heart disease, mitral and tricuspid stenosis, adherent pericarditis, subacute verrucous endocarditis of the tricuspid, mitral and aortic valves, hypertrophy and dilatation (marked) of the left auricle, dilatation and hypertrophy (slight) of the right side of the heart, massive embolization of the pulmonary arteries, pulmonary congestion and edema, bilateral pleural effusion (3 ounces [90 cc]), ascites (5 ounces [150 cc]), chronic congestion of the spleen, kidneys, lungs and pancreas, fatty changes in the liver, adenoma of the thyroid gland, with cystic degeneration, and endarteritis of the cerebral vessels, with cerebral atrophy and multiple areas of encephalomalacia.

REVIEW OF DATA

Type of Lesion—Primary isolated lymphogranuloma of the small intestine is rare. Fischer, in 1913, is credited with being the first to describe this condition.

Catsaras and Geogantas described a case in which a clinical diagnosis of intestinal obstruction had been made and in which the condition was found to be due to a large nodule in the ileocecal region. Histologic examination of the specimen pointed to a diagnosis of lymphogranulomatosis. The patient died several months later, but permission for post-mortem examination was not obtained.

Several cases in which isolated lymphogranulomatous lesions of the bowel were discovered at operation and successfully resected have been described,¹⁵ in others the lesion was discovered at necropsy.¹⁶

In the cases in which operation was performed (including cases in which the patients were alive at the time of publication of the articles¹⁵

15 de Groot, Biebl, Sussig, Heilmann, Pamperl and Terplan and Pissarewa

16 Wahlgren, Goedel, Hanneborg, Wald and Sussig

and those cases in which the patients died after surgical intervention without postmortem examination¹⁷) the lesions cannot be strictly classified as isolated, because the extent of the disease was determined only by laparotomy, which does not include a detailed pathologic examination

Diffuse involvement of the small bowel, with no evidence of disease elsewhere, was observed by several investigators¹⁸ In the case reported on by Sussig only the large and small intestines were involved

Incidence—In an analysis of seventy-five cases of gastro-intestinal lymphogranulomatosis reported in the literature and the present two cases it was found that over 50 per cent of the cases occurred in patients between the ages of 40 and 60, 10 per cent in patients between the ages of 60 and 70 and the remainder in patients of other age periods The largest individual group of patients were between 50 and 60 years old Men formed the majority of the patients, in a ratio of almost two to one

History and Symptoms—With the gastric type of lesion the chief symptoms were epigastric pain and distress of varying severity after meals, vomiting and nausea, eructations of gas, weakness and loss of appetite and weight There might be hematemesis and melena The duration of symptoms varied from a short time to several years with remissions In the case of gastric involvement reported here the duration was of several weeks only

Physical examination usually revealed no abnormality, except for occasional emaciation A palpable mass was uncommon but was observed in some cases¹⁹ No mass was observed in our patient The liver and spleen usually were not palpable Superficial glandular enlargement was infrequent

Achlorhydria is not a constant finding but was present in our patient and in others²⁰

The diagnosis usually made was carcinoma or ulcer of the stomach The former diagnosis was made more frequently

The intestinal type of lesion was characterized by the following symptoms increased malaise, weakness, loss of weight, loss of appetite and the predominance of abdominal symptoms, namely, abdominal pain, meteorism, diarrhea, constipation or alternating diarrhea and constipation Melena was not common

17 Ringdal, Wahlgren and Catsaras and Georgantas

18 Eberstadt, Partsch and Oglobina

19 Terplan, Hayden and Apfelbach, von Redwitz, David and Tschilow

20 Scott and Forman, de Groot, Novotny, Sussig, Hayden and Apfelbach, von Redwitz and Kopstein

Physical examination sometimes revealed a palpable resistance or a mass in the abdomen. Irregular bouts of fever were occasionally present.

Examination of the blood frequently showed secondary anemia, with polymorphonucleosis and leukopenia. In some cases there was slight eosinophilia. In the cases reported on by Wald and Hanneborg there was marked eosinophilia. Tschilow noted monocytosis in his case.

The symptoms with the intestinal type of lesion appeared in two forms: (1) the inflammatory symptoms—the diagnosis usually being tuberculous enterocolitis—and (2) the obstructive symptoms—the diagnosis commonly being carcinoma.

Complications, such as hemorrhage, intussusception and perforation, have already been described. Ascites was noted in some cases.²¹ Coronini observed jaundice in a case of gastrolymphogranulomatosis, which on postmortem examination was observed to be due to enlargement of the regional glands at the porta hepatis.

Roentgen Aspect—The roentgen appearance in the gastric type of lesion, as observed by Holmes, Dresser and Camp, did not differ from that of carcinoma, except that in some cases peristalsis was not interfered with to the extent generally seen in carcinoma. The diagnosis based on the roentgen findings was carcinoma of the stomach in five cases and lymphoblastoma in one case (in which biopsy was performed).

Kaznelson, in 1924, described a case in which pyloric stenosis and niche formation were noted and in which a diagnosis of gastric ulcer, possibly malignant, was made. He stated on review of the case after postmortem examination that increase of a gastric niche, with fever, malaise and diarrhea, should suggest the presence of lymphogranulomatosis not only of the stomach but of the intestine as well.

Junghagen described two types in which lymphogranulomatosis occurred in the stomach, first, as a manifestation of the generalized form of Hodgkin's disease and, second, as a localized form of the disease, the so-called neoplastic type. In the first type the roentgen findings were similar to those of ulcer. The ulcer usually enlarged and aroused the suspicion of malignancy. In the second type the process was generally localized to the pyloric canal and caused stenosis of the lumen. The author pointed out, however, that when the muscular layer had been infiltrated only partially by the lymphogranulomatous tissue to produce a filling defect, definite peristaltic waves were noted passing over the region of the lesion. In other respects the roentgen appearance conformed to that of carcinoma.

21 Weinberg, Coronini and Sussig

Ruggles and Stone claimed that there is no type of lesion or region of involvement characteristic of the disease and that therefore there is no characteristic picture. When gastric peristalsis persists and there is a lesion of the stomach, this lesion is most likely to be a lymphoblastoma.

In the majority of cases the roentgen diagnosis was carcinoma of the stomach, and in a few instances, ulcer. The pylorus was the region frequently involved.

Review of the literature shows that the roentgen findings in the intestinal type of Hodgkin's disease are meager. There is apparently no specific form of roentgen diagnosis. The clinical picture is one usually of enteritis or obstruction of the bowel. In the second case reported here the roentgenograms showed irregular constrictions and dilatations of the small bowel, which were interpreted as due to non-specific ulcerative enteritis, but these findings were no different from those usually observed in cases of tuberculous peritonitis or intestinal malignant growth.

In a review of the records of the Mount Sinai Hospital three cases were found which might be interpreted as instances of localized gastro-intestinal Hodgkin's disease, the reports are not given here in detail because complete examinations were not made.

Treatment—Holmes, Dresser and Camp have shown the striking effects of roentgen therapy on lymphoblastomas. They recorded the case of a woman aged 64 who had been receiving roentgen treatment for enlarged peripheral glands which had proved on biopsy to contain a malignant lymphoma. Later, gastric symptoms developed. A gastro-intestinal examination revealed a filling defect involving the lower third of the stomach. The patient received a course of roentgen radiation. Two months later roentgen examination of the stomach showed that the filling defect had markedly diminished in size and that peristaltic waves passed over without interruption. Ruggles and Stone strongly advised roentgen therapy for lymphoblastoma.

Sussig, Singer and other writers have advocated surgical resection combined with roentgen therapy for localized lymphogranulomatous lesions of the gastro-intestinal tract. Vasiliu, Steindl, Froboese and others, as pointed out early in this paper, have reported on patients who underwent resection of the lesions successfully and who were alive from several months to several years after operation. When the lesions are inoperable or surgical intervention is contraindicated, roentgen therapy is advocated for the amelioration of symptoms and prolongation of life.

SUMMARY

Two cases of gastro-intestinal lymphogranulomatosis are reported. A review of seventy-three reports of cases selected from the literature has been made to evaluate the various manifestations of the disease.

The disease usually simulates one of four main clinical entities (a) gastric carcinoma, (b) gastric ulcer, (c) enterocolitis or (d) obstruction of the bowel

There are no specific roentgen findings typical of the condition

The characteristics of generalized Hodgkin's disease, for example superficial glandular enlargement, enlargement of the liver and spleen and hematologic changes, are usually absent

The diagnosis is established after operation or at necropsy, rarely by biopsy. The microscopic changes may at times be difficult to differentiate from those of lymphosarcoma

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IMMEDIATE EFFECT OF TINCTURE OF DIGITALIS ON EMPTYING TIME OF HUMAN STOMACH

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It has been suggested by various authors that digitalis causes an increase in gastric and intestinal motility. In the volume by Meyer and Gottlieb¹ entitled "Experimental Pharmacology," work (which was done in 1906) is reported on to the effect that digitalis glucosides influence gastric and intestinal peristalsis. Vail² by means of the roentgen ray observed that digitalis increased gastric motility. Cloetta³ stated that digitalis causes an increased gastric secretion. Since Hellebrandt⁴ has shown that gastric secretion and motility run parallel (at least during fasting), the observation of Cloetta is significant. A rather careful review of the literature, however, has failed to disclose any well controlled experiments which conclusively demonstrated that digitalis actually decreased the emptying time of the stomach. It was therefore thought worth while to investigate this problem. Material and data⁵ were at hand which facilitated the execution of this study.

METHODS

In seven healthy male medical students the normal emptying time of the stomach was determined fluoroscopically. The standard meal was the same as that reported on previously⁶. Fifteen grams of farina and 1 Gm of salt were added to 350 cc

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This research was made possible through a grant from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association

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3 Cloetta, cited by Bastedo, W A. Materia Medica, Pharmacology and Therapeutics, Philadelphia, W B Saunders Company, 1933, p 208

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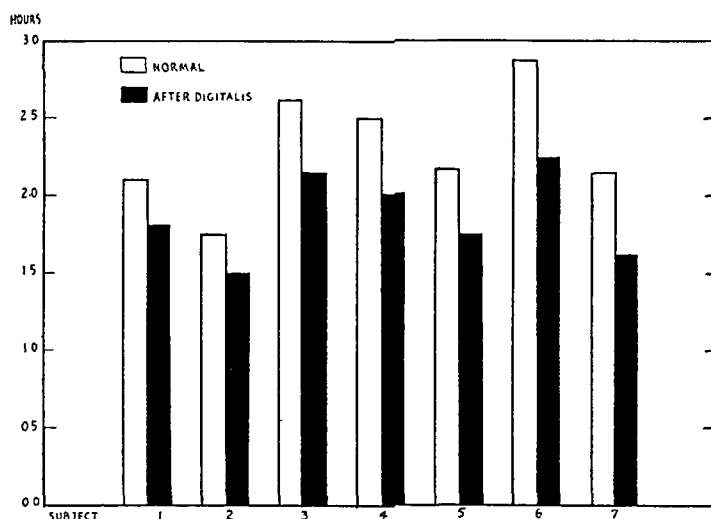
6 Van Liere, E J, Lough, D H, and Sleeth, C K. The Effect of Ephedrine on the Emptying Time of the Human Stomach, J A M A **106** 535 (Feb 15) 1936

of water and boiled down to a volume of 200 cc. Fifty grams of barium sulfate was added so that the position of the meal could be determined with the fluoroscope. A number of control observations were made for each subject. The average of these figures was used for the norm.

The effect of tincture of digitalis on the emptying time of the stomach was then studied. Five cubic centimeters of fresh tincture of digitalis was thoroughly mixed with the standard meal. The emptying time of the stomach was again determined fluoroscopically. Careful attention was given, of course, to all details essential for well controlled experimental conditions.

RESULTS

The accompanying chart and table show the results obtained. In the seven subjects digitalis decreased the emptying time of the stomach an average of 18.5 per cent. The greatest decrease noted in the emptying time was 24.6 per cent and the least 12.9 per cent.



The effect of 5 cc. of tincture of digitalis on the emptying time of the human stomach.

The Effect of Five Cubic Centimeters of Tincture of Digitalis on the Emptying Time of the Human Stomach

Subject	Normal		After Digitalis		Decrease, Percentage
	Number of Tests	Average Emptying Time, Hours	Number of Tests	Average Emptying Time, Hours	
1	5	2.10	3	1.82	12.9
2	3	1.75	2	1.50	14.3
3	6	2.62	3	2.15	17.9
4	11	2.50	3	2.02	19.1
5	9	2.17	2	1.75	19.4
6	4	2.87	2	2.25	21.6
7	5	2.15	2	1.62	24.6
Average	6	2.31	2.4	1.87	18.5

COMMENT

It is generally known that digitalis is capable of exerting both a general and a local action. The increased gastric motility may have been produced by either mode of activity, that is, it may have been caused by stimulation of the vagus nerve by way of the medulla or by local irritative action. It is difficult, unfortunately, to separate the two actions, if, for example, atropine is administered to paralyze the vagus nerve, gastric motility is greatly reduced. Furthermore atropine could, by its side effects, introduce other undesirable factors. There is, however, some more or less indirect evidence on this point.

Alvarez⁷ demonstrated that if isolated strips of different parts of the intestinal tract were immersed in Locke's solution containing a 1:200 dilution of tincture of digitalis, the strips excised from the duodenum and jejunum showed depression and those excised from the ileum and colon showed a moderate amount of stimulation. The depression of the strips from the duodenum and jejunum was not due to the alcoholic content of the tincture of digitalis, for this factor was controlled by immersing strips in Locke's solution which contained a given amount of alcohol. While work was not reported on the effect of tincture of digitalis on strips excised from the stomach, the fact that strips from the duodenum and jejunum showed depression makes it permissible to assume that the work reported on by Alvarez may be interpreted to show that the local irritative action of digitalis is less likely to produce hypermotility of the stomach than is its central action.

It is probably safe to assume that the central action of digitalis has the same effect on the small intestine as on the stomach, since the vagus nerve is the motor nerve to both structures. Further, if Alvarez' gradient theory of gastro-intestinal movement is accepted, the hypermotility of the stomach aggravated by digitalis would in turn cause the peristalsis of the small intestine to be more active, and this might well explain, in part at least, the diarrhea which often accompanies the administration of digitalis, particularly if the drug is given in large doses.

As alcohol is known to influence the emptying time of the stomach, it was necessary to control this factor. Several of the subjects were given standard meals which contained 5 cc of 70 per cent alcohol, that is, approximately the same amount of alcohol as was contained in the previously administered dose of digitalis. It was found that this small dose of alcohol had no effect on the emptying time of the stomach.

The criticism might be raised that a decrease of 18.5 per cent in the emptying time of the stomach is not particularly significant. This may be partially true if the subject eats a small meal or one which leaves

⁷ Alvarez, W. C. Differences in the Action of Drugs on Different Parts of the Bowel, *J. Pharmacol. & Exper. Therap.* **12**: 171 (Oct.) 1918.

the stomach quickly, such as the standard meal used in performing the experiments reported in this paper. If a larger meal is ingested, however, or one which contains a good deal of protein or fat, a decrease of 18.5 per cent becomes more significant. Such a meal, for example, would probably take from five to six hours to leave the stomach, if it is permissible to assume that digitalis continues to exert the same influence on gastric motility in the case of a large meal as it does with the small one, the emptying time would be decreased well over an hour.

The fact that tincture of digitalis is capable of decreasing the emptying time of the stomach is of interest, as a review of the literature discloses that while a number of substances delay the emptying time, not many are known which hasten it. From the data set forth in this paper, moreover, it is safe to assume that digitalis may be administered orally after a meal without any deleterious effect on gastric motility. Since it has been shown conclusively that anoxic states are capable of delaying the emptying time,⁸ the results reported in this paper are of practical interest, for digitalis is often administered during anoxic conditions which have been brought about by disease of the heart or lungs.

SUMMARY AND CONCLUSIONS

It was found that 5 cc of tincture of digitalis when mixed with a standard test meal (consisting principally of 15 Gm of farina) decreased the normal emptying time of the stomach on an average of 18.5 per cent in seven healthy young men. The results all lay in the same direction, and there were no exceptions. In no case was the decrease in the emptying time less than 12.9 per cent, and the greatest decrease noted was 24.6 per cent.

The conclusions which may be drawn from the work reported here are as follows. Tincture of digitalis administered in doses of 5 cc is capable of decreasing the emptying time of the stomach of the average person about 18 per cent, as based on experiments performed on seven subjects. It may thus be given immediately before or directly after a meal without any deleterious effect on gastric motility. Experimental evidence is offered which throws light on the causation of the diarrhea which often accompanies the administration of digitalis. Finally, since digitalis is often given in conditions associated with anoxemia, which has been shown to inhibit gastric motility, the fact that it is capable of decreasing the emptying time of the stomach is of practical importance.

⁸ Van Liere, E. J., Lough, D. H., and Sleeth, C. K. Effect of Anoxemia on the Emptying Time of the Human Stomach. Influence of High Altitudes, *Arch Int Med* **58** 130 (July) 1936.

UREA CLEARANCE IN PERNICIOUS ANEMIA

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During studies on the excretion of hippuric¹ acid and xylose² of patients with pernicious anemia the renal function was estimated by means of the urea clearance test. The apparent importance of renal function to the clinical status of the patients led us to make additional studies of the urea clearance of these and other patients with pernicious anemia.

Mosenthal³ stated that in cases of severe anemia, whether of the primary or of the secondary type, results were obtained with the test meal (Mosenthal test) which were similar in every detail to those that have been described in cases of advanced contracted kidney. He further stated that from the functional changes alone one would be warranted in considering the prognosis grave but that the cure of the severe anemia might be followed by great functional improvement. Kahn and Barsky⁴ found that in three cases of pernicious anemia the renal function was normal, as evidenced by the phenolsulfonphthalein test and the blood nitrogen partition. The urinary nitrogen partition also was normal except that the oxyproteinic nitrogen fraction was increased to twice normal. Gettler and Lindeman⁵ stated that the urea nitrogen content of the blood was above normal in only 18 per cent of the cases of pernicious anemia, being within normal limits (10 to 20 mg) in the remainder, but even in these the tendency toward the higher normal limits was noticeable. They stated that this was probably due not to a

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3 Mosenthal, H O. Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, *Arch Int Med* **16** 733-774 (Nov) 1915.

4 Kahn, M, and Barsky, J. Studies of the Chemistry of Pernicious Anemia *Arch Int Med* **23** 334-345 (March) 1919.

5 Gettler, A O, and Lindeman, E. Blood Chemistry of Pernicious Anemia *Arch Int Med* **26** 453-458 (Oct) 1920.

permanent renal lesion but to the decreased amount of circulating blood

The aforementioned reports on renal function in pernicious anemia were published previous to the advent of liver therapy. It is our purpose in this paper to report one hundred and eighty determinations of the urea clearance of eighty-eight patients with pernicious anemia. Whenever possible determinations were made before and after institution of specific therapy.

METHOD

The patients with pernicious anemia who were studied had been followed in this department for varying periods up to nine years. Only the patients who maintained normal red blood cell counts for at least eighteen months while taking 3 vials of liver extract or 12 capsules or less of a liver-stomach concentrate daily by mouth were classified as easy to maintain with a normal red blood cell count. Those requiring larger amounts of oral therapy or liver extract by injection were classified as difficult to maintain. The Van Slyke method was used in determining the urea clearance. Examination of urine in most cases revealed no abnormality. Many of the women patients, however, showed a trace of albumin and varying numbers of pus cells.

RESULTS

The urea clearance of fifty patients was determined during a relapse. The values varied from 31 to 125 per cent of normal, averaging 62.5 per cent. However, two patients who were not examined until after a partial remission had been induced by liver extract had urea clearance values of 23 and 29 per cent of normal, respectively. These patients were not included in the group of those showing a relapse. The urea nitrogen content of the blood varied from 7.9 to 28.4 mg per hundred cubic centimeters. There were, however, only five patients who showed a urea nitrogen value over 23 mg per hundred cubic centimeters, the upper limit of normal.

Twenty-two of the patients showing relapse were receiving the diet recommended in "the Pharmacopoeia of the United States of America" for patients used in the standardization of liver extract or were receiving the diet used by us⁶ in studies on the intrinsic factor of liver extract. These diets are low in protein. It has been shown⁷

6 Helmer, O. M., Fouts, P. J., and Zerfas, L. G. Increased Potency of Liver Extract by Incubation with Human Gastric Juice, *Proc Soc Exper Biol & Med* **30** 775-778 (March) 1933.

7 Jolliffe, N., and Smith, H. W. The Excretion of Urine in Dogs. II. The Urea and Creatinine Clearance on Cracker Meal Diet, *Am J Physiol* **99** 101-107 (Dec) 1931. Cope, C. L. Studies of Urea Excretion. VIII. The Effects on the Urea Clearance of Changes in Protein and Salt Contents of the Diet, *J Clin Investigation* **12** 567-572 (May) 1933. Goldring, W., Razinsky, L., Greenblatt, M., and Cohen, S. The Influence of Protein Intake on the Urea Clearance in Normal Man, *ibid* **13** 743-748 (Sept) 1934. Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S. The Relationship of the Urea Clearance to the Renal Blood Flow, *Am J Physiol* **110** 387-391 (Dec) 1934.

that a diet low in protein decreases the urea clearance of dogs and of human beings. Our average values were perhaps decreased by the diet low in protein. However, examination of table 1 shows that the distribution of patients receiving the low protein diet in the various clinical groups tended to minimize rather than accentuate the differences in the groups.

TABLE 1—*Average Values for Urea Clearance and Distribution of Values for Various Clinical Groups of Patients with Pernicious Anemia During a Relapse and During a Remission*

	Num ber of Pa tients	Num ber of Ex am ina tions	Average Urea Clear ance, Per cent age of Normal	Number of Patients with Urea Clearance		Number of Patients with	
				Less Than 75% of Normal	More Than 75% of Normal	Less Than 50 Gm of Protein in Diet	More Than 50 Gm of Protein in Diet
1 All patients during relapse	50	52	62.5	39	11	22	28
a Having early involvement of spinal cord	31	32	67.2	21	10	15	16
b Having advanced involvement of spinal cord	19	20	53.0	18	1	7	12
c Under 60 years of age	28	28	62.9	21	7	13	15
d Over 60 years of age	22	24	60.3	18	4	9	13
e Having no known complication	30	30	63.5	22	8	14	16
f Having complications, such as arteriosclerosis and infections	20	22	59.2	17	3	8	12
g Difficult to maintain with normal red blood cell count	20	21	61.1	17	3	7	13
h Easy to maintain with normal red blood cell count	9	10	75.7	4	5	4	5
2 All patients with normal red blood cell count	61	75	79.1	29	32		
a Having early involvement of spinal cord	37	44	86.1	14	23		
b Having advanced involvement of spinal cord	24	31	71.5	15	9		
c Under 60 years of age	35	43	85.1	14	21		
d Over 60 years of age	26	32	70.7	15	11		
e Having no known complication	33	40	83.3	14	19		
f Having complications, such as arteriosclerosis and infections	28	35	74.4	15	13		
g Difficult to maintain with normal red blood cell count	26	34	73.3	13	13		
h Easy to maintain with normal red blood cell count	17	23	93.8	6	11		

As seen in table 1 the patients with the more advanced involvement of the central nervous system showed distinctly lower average values for urea clearance than did the patients with only slight involvement. There was also a tendency for the older patients and the patients having degenerative or infectious complications to have lower values for urea clearance. The patients for whom it was difficult to maintain a normal red blood cell count by oral therapy likewise had a distinctly lower average value for urea clearance than did those for whom it was easy to maintain a normal red blood cell count.

Sixty-one patients were examined when the red blood cell count was normal. They were seen in the outpatient department at the time of the determination of the urea clearance, and consequently their exact diets were not known. However, owing to the poor financial status of most of the patients the intake of protein probably was not high. The average value for urea clearance for this group of patients was 79.1 per cent (the values varying between 39 and 156 per cent of normal). Table 1 again reveals that the older patients, those with more advanced involvement of the spinal cord and those with degenerative or infectious complications had a distinctly lower average value for urea clearance than the younger patients and those who did not have these complicating factors. Patients with these complications have been shown⁸ to require more liver orally, and there were even greater differences in the urea clearance values for the patients for whom it was difficult to maintain a normal red cell count with oral therapy and for those for whom it was easy to maintain a normal red cell count. None of the seventeen patients for whom it was easy to maintain a normal red cell count had a value for urea clearance below 50 per cent, and only six had values below 75 per cent. This is in contrast to the discovery of five patients having urea clearance values below 50 per cent in the group for whom it was difficult to maintain a normal red cell count. In addition, thirteen of the twenty-six patients in this group had urea clearance values below 75 per cent of normal.

In comparing the findings for the patients during a relapse with those for patients having normal red blood cell counts, it is evident that the average value for urea clearance was higher for the patients having normal red blood cell counts. It was not possible to examine all patients listed in table 1 both during a relapse and during a remission, so the groups are not identical. Table 2 shows the urea clearance of the thirty-seven patients for whom determinations were made both during a relapse and after treatment. It is evident from table 2 that the differences in the values for urea clearance before and after treatment shown in table 1 were not due to the inclusion of patients not studied in both groups.

Table 3 shows individual clearance values for a group of fifty patients determined at different red blood cell levels. In many instances the urea clearance value obtained when the patient showed a relapse was in no way indicative of the actual renal function of the patient after the blood count became normal. In some the increase in urea clearance was progressive from the start of therapy, and in others it

⁸ Beebe, R. T., and Lewis, G. E. The Maintenance Dose of Potent Material in Pernicious Anemia, *Am J M Sc* **181** 796-812 (June) 1931. Fouts, P. J., and Zerfas, L. G. Maintenance Dosage of Liver Extract in the Treatment of Pernicious Anemia, *Ann Int Med* **6** 1298-1304 (April) 1933.

did not occur until later. The elevation in the urea clearance value followed the increase in the protein content of the diet in several instances, but in others there was an elevation in spite of the fact that the patients continued to receive a diet low in protein. An increase in the protein content of the diet was not always followed by a rise in the value for urea clearance. In other instances the protein content of the diet was not low at the time of the first examination, yet there was an elevation in the value for urea clearance after the red

TABLE 2—*Average Values for Urea Clearance of Patients with Pernicious Anemia Determined Both Before and After Treatment*

	No. of Patients	Average Urea Clearance, Percentage of Normal	No. of Patients with Urea Clearance Less than 75% of Normal	No. of Patients with Urea Clearance More than 75% of Normal
1 Total number of patients	37			
a Relapse	37	59.9	30	7
b Remission	37	74.9	19	18
2 Patients with early involvement of spinal cord				
a Relapse	22	65.4	16	6
b Remission	22	77.1	10	12
3 Patients with advanced involvement of spinal cord				
a Relapse	15	51.9	14	1
b Remission	15	71.9	9	6
4 Patients under 60 years of age				
a Relapse	25	62.6	19	6
b Remission	25	80.7	10	15
5 Patients over 60 years of age				
a Relapse	12	54.5	11	1
b Remission	12	63.3	9	3
6 Patients with no known complications				
a Relapse	26	62.4	20	6
b Remission	26	77.5	12	14
7 Patients with complications, such as arteriosclerosis and infections				
a Relapse	11	54.2	10	1
b Remission	11	69.7	7	4
8 Easy to maintain with normal red blood cell count				
a Relapse	6	72.1	3	3
b Remission	6	82.1	2	4
9 Difficult to maintain with normal red blood cell count				
a Relapse	15	59.5	13	2
b Remission	15	71.1	9	6

blood cell count reached normal. The first patient had the lowest value (35 per cent) for urea clearance, which later increased to normal. Patients with a urea clearance value below 50 per cent of normal as often had a normal value after therapy as those who had a value between 50 and 70 per cent of normal during a relapse. In general it could not be determined from the clinical status of the patient whether there would or would not be an increase in urea clearance after the rise in the red blood cell count. However, it can be stated that if the urea clearance value is low the patient is more likely to require liver extract by injection to maintain a normal red blood cell count than if the urea clearance value is normal. There did not seem to be any relation between the blood pressure and the urea clearance of the patient during a relapse.

TABLE 3—Urea Clearance Determinations for Fifty Patients with Pernicious Anemia at Various Red Blood Cell Levels

Case No	Age	Date	Red Blood Cells, Millions	Hemo globin, %	Urea Clearance, % of Normal	Involve ment of Central Nervous System	Compli cations	Mainte nance*	Blood Urea Nitrogen, Mg per 100 Cc	Protein Content of Diet, Gm
1	36	7/22/36	0 70	22	35	+	—	?	8 0	31
		7/29/36	1 00	27	58				9 5	23
		8/27/36	2 97	43	67				10 0	
		12/18/36	5 24	86	97				9 7	
2	46	11/ 3/36	0 82	25	56	—	—	?	11 9	27
		12/18/36	3 57	70	64				7 1	31
		2/12/37	4 08	88	57				14 7	
3	59	7/24/36	1 00	28	51	++	—	?	15 7	31
		7/29/36	0 89	25	51				15 2	24
		8/26/36	2 94	51	31				13 8	31
		11/10/36	4 08	83	57				12 2	
		2/12/37	4 67	94	47				12 3	
4	45	3/23/37	0 91	25	58	—	+	?	7 9	20
		4/16/37	2 79	52	66				5 7	57
		6/ 4/37	4 61		99				8 4	
5	44	4/20/36	0 96	25	99	—	—	I	12 1	27
		11/ 9/36	4 79	94	80				13 0	
6	58	5/29/36	1 04	20	38	+++	—	D	26 3	40
		8/24/36	4 07	75	53				16 6	
		4/ 2/37	4 15	91	52				13 7	
7	57	2/ 5/36	1 06	31	41	+++	—	?	23 3	
		3/11/36	3 30	64	68				17 2	
		5/ 8/36	5 39	88	84				16 1	
8	61	7/ 6/36	1 09	29	58	++	++	D	16 7	70
		8/25/36	3 21	82	87				15 6	67
9	57	4/ 7/36	1 14	28	50	+	—	I	15 4	30
		4/24/36	1 65	36	34				8 1	39
		6/ 2/36	4 58	70	56				14 6	
10	59	1/ 8/37	1 16	30	58	++	++	?	10 4	20
		2/ 4/37	3 44	73	80				6 3	70
11	62	2/26/37	1 17	35	69	+++	+	?	14 5	25
		4/15/37	3 62	77	61				9 9	68
		5/12/37	4 78	102	55				15 6	56
12	51	5/27/36	1 24	38	53	+	—	?	17 8	52
		9/ 1/36	4 15	91	57				13 9	
		11/11/36	5 33	103	67				13 5	
13	56	4/16/36	1 26	38	74	++	—	I	14 7	68
		6/11/36	3 62	73	72				11 5	72
14	44	12/ 3/36	1 33	37	65	—	—	D	9 0	15
		12/23/36	2 88	56	48				6 8	71
		2/ 2/37	5 26	98	54				9 9	
15	59	7/ 3/35	1 35	44	125	—	—	E	14 3	55
		9/16/36	4 26	86	85				11 3	
16	26	3/23/37	1 43	46	52	—	—	?	12 9	21
		4/20/37	1 98	52	53				10 3	38
		5/13/37	3 47	77	81				10 5	80
17	31	6/19/36	1 44	33	92	—	—	?	18 3	70
		11/11/36	5 04	106	88				17 7	
18	70	3/24/36	1 45	43	42	+	—	?	14 7	68
		4/20/36	3 25	69	50				12 4	65
		9/ 1/36	4 43	89	42				12 1	
19	58	5/14/35	1 52	44	75	+++	+	?	8 0	60
		10/15/35	4 54	97	112				7 0	
20	70	8/25/36	1 60	45	31	+	—	I	10 5	32
		9/24/36	3 82		65				10 4	33
		11/ 9/36	4 72		62				8 5	
21	62	9/21/34	1 64	44	39	+++	+	D	25 7	60
		11/22/34	3 97	86	44				21 2	67
22	61	5/11/37	1 64	47	54	—	—	?	19 8	26
		6/23/37	3 23	85	56				15 8	21
		7/ 2/37	3 84	92	64				12 7	59
23	36	7/30/36	1 84	41	47	—	—	D	13 5	27
		8/26/36	2 98	66	48				5 8	22
		11/10/36	4 60	92	75				8 5	
24	41	5/28/35	1 87	46	58	+++	—	?	8 8	75
		12/16/35	5 24	115	150				9 7	

* I indicates easy to maintain with a normal red blood cell count with orally administered liver. D difficult to maintain with a normal red blood cell count, i e., injections of liver extract required.

TABLE 3—Urea Clearance Determinations for Fifty Patients with Pernicious Anemia at Various Red Blood Cell Levels—Continued

Case No	Age	Date	Red Blood Cells, Millions	Hemoglobin, %	Urea Clearance, % of Normal	Involve ment of Central Nervous System	Complications	Maintenance	Blood Urea Nitrogen, Mg per 100 Cc	Protein Content of Diet, Gm
25	64	5/ 6/35 11/12/35	1 91 3 93	53 77	54 83	+++	+	D	19 2 13 7	71
26	63	10/15/36 10/29/36 1/ 4/37	1 94 2 81 4 56	63 72 86	57 55 63	+	—	D	15 8 9 6 9 8	22 26
27	59	8/28/36 10/ 5/36 12/ 3/36	1 95 3 50 4 40	58 83 89	31 38 39	++	—	?	11 9 9 8 7 3	31 30
28	64 66	6/11/34 4/ 7/36 4/20/37	3 06 2 03 4 63	74 51 113	77 115 111	+	—	D	8 4 10 0 9 1	104 64
29	54	10/ 2/36 11/12/36	2 06 4 12	49 96	71 71	++	—	?	15 6 14 1	282 72
30	45	5/ 5/36 8/31/36 12/ 7/36	2 09 4 15 4 76	51 86 92	70 90 117	—	—	D	18 6 15 8 16 2	70
31	72	11/ 7/35 11/26/35 1/ 2/36 6/15/36 6/ 8/37 7/ 2/37	2 10 2 03 4 11 4 87 2 39 3 44	64 62 87 89 74 89	39 36 36 54 32 44	+	+	D	28 4 15 8 15 2 17 0 25 9 16 5	66 70 21 68
32	67	11/29/35 2/26/37 4/15/37	2 12 2 70 3 50	65 71 92	84 86 80	+	++	E	15 4 13 5 12 1	30 29
33	56 57	8/ 2/34 10/31/35	2 17 5 28	50 120	79 105	—	—	E	15 0 17 2	101
34	58	5/21/35 11/ 5/35	2 19 5 12	59 103	49 105	—	—	E	17 5 12 6	61
35	56	6/ 4/35 9/19/35	2 19 5 41	65 113	60 70	+++	+	D	12 0 12 0	57 66
36	40 42	11/16/34 9/10/36 12/ 4/36	2 25 3 97 4 21	57 83 83	110 79 91	—	—	D	14 5 9 3 10 0	70
37	51	1/14/36 8/25/36	2 36 3 89	75 76	51 65	++	—	D	12 8 12 6	57
38	64	2/21/36 8/31/36	2 41 4 72	70 97	57 50	—		D	14 9 8 7	59
39	65 66	10/30/34 10/17/35	2 95 4 58	79 94	51 52	++	+	D	12 3 11 6	55
40	35	10/23/34 10/ 8/35 2/17/36 12/15/36	3 26 5 00 4 99 5 20	84 86 87 79	46 44 45 45	++	+	D	15 8 12 6 17 7 14 8	60
41	66 68	4/30/35 10/13/36	3 42 3 39	75 74	33 57	++	+++	D	6 8 8 0	55 68
42	41	1/ 8/37 4/19/37	3 69 4 48	82 94	61 60	+++	+	?	10 8 7 8	
43	82	12/17/35 1/20/36 2/ 3/36 5/15/36	3 82 4 98 5 05 5 09	75 92 81 87	23 36 43 40	+++	++	D	30 8 22 1 19 6 19 1	62 65
44	50	9/13/34 10/22/35	4 22 4 59	67 86	72 97	+	+	D	11 4 15 2	
45	52	9/ 5/35 10/10/35 1/22/36 3/ 5/36	4 54 4 13 4 40 4 38	97 92 92 83	36 38 41 49	—	+++	D	6 8 19 1 12 7 14 6	
46	74	8/16/34 3/ 9/36	5 81 5 18	97 107	61 70	++	+	E	17 4	
47	66	11/ 3/36 12/14/36 4/19/37	3 48 3 94 4 98	96 87 107	71 51 58	+	+	?	18 3 13 9	30 30
48	60	12/10/36 2/ 1/37	3 76 4 34	92 92	45 81	+++	+	?	15 3 11 3	22 47
49	67 68	12/27/35 5/12/37 6/17/37	3 19 1 50 3 26	64 42 70	63 38 57	++ ++	+	?	15 6 19 8 16 0	21 73
50	46	4/28/37 6/ 3/37	1 34 2 97	36 61	40 61	—	—	D	8 9 10 7	17 40

CONCLUSIONS

There may be a marked increase in the urea clearance of the patient with pernicious anemia after a remission induced by liver extract.

The rise in the value for urea clearance following the induced remission cannot be predicted from a study of the clinical condition of the patient.

The patient having the complicating factors usually associated with an increased requirement of orally administered liver extract is likely to show a low value for urea clearance even after the red blood cell count reaches normal.

The patient with a low value for urea clearance is more likely to require liver extract by injection to maintain a normal red blood cell count than is the patient with a normal value for urea clearance.

EXPERIMENTAL ENDOCARDITIS DUE TO STREPTOCOCCUS VIRIDANS

BIOLOGIC FACTORS IN ITS DEVELOPMENT

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There are two distinct main aspects to the consideration of subacute bacterial endocarditis: (1) the mode of infection of the cardiac valves and (2) the factors involved in the continuance of the growth on the valve. The second aspect was the subject of the present investigation. We felt that it might prove to be of practical value to discover why infection due to a relatively nonvirulent organism persists on the cardiac valves. To this end the behavior of *Streptococcus viridans* was noted in various types of serum and whole blood, and the fate of the bacterium was investigated when placed in the blood stream, on a cardiac valve and in certain other tissues of the normal living dog.

Horder,¹ Schottmüller,² and Libman and Celler³ first observed the morphologic characteristics of *St. viridans* and noted its relative nonvirulence. Since their observations innumerable studies have been made of the bacteriologic and immunologic aspects of the disease. It appears from studies both of patients suffering from the disease⁴ and of animals

Aided by the A. D. Nast Fund for Cardiac Research

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1 Horder, I. *Quart. J. Med.* **2**: 289, 1908-1909

2 Schottmüller, H. *München med. Wchnschr.* **57**: 617, 1910

3 Libman, E., and Celler, H. L. *Am. J. M. Sc.* **140**: 516, 1910

4 (a) Kinsella, R. A. *Bacteriologic Studies in Subacute Streptococcus Endocarditis*, *Arch. Int. Med.* **19**: 367 (March) 1917. (b) Wright, H. D. *J. Path. & Bact.* **28**: 541, 1925. (c) Levine, S. A. *Clinical Heart Disease*, Philadelphia, W. B. Saunders Company, 1936, p. 195. (d) Kredler, W. A. *J. Infect. Dis.* **39**: 186, 1926

having endocarditis⁵ that the immune properties of the blood are increased against the particular strain of streptococcus infecting the cardiac valve

Harbitz⁶ was probably the first to describe clearly the clinical and pathologic picture which develops when the cardiac valves are the seat of bacterial infection. He differentiated the acute ulcerative type of endocarditis from the subacute proliferative type both clinically and pathologically. Indeed, his morphologic observations were so exhaustive and accurate that relatively few new facts have been added since. Horder¹ later observed that the organism in patients with the subacute infection was almost always a streptococcus of low virulence and in many instances was identical with the streptococcus found in the alimentary canal. Libman and Celler,³ as well as Schottmüller,² showed conclusively on the basis of pathologic, bacteriologic and clinical studies that *Str. viridans* is the etiologic agent in the majority of cases of subacute bacterial endocarditis.

Ribbert⁷ was the first to produce bacterial endocarditis experimentally, he injected intravenously staphylococci mixed with finely ground particles of potato. Rosenbach⁸ also produced endocarditis of an acute type by injuring the aortic leaflets and subsequently inoculating them with bacteria. Horder¹ was probably the first to produce the *Str. viridans* type of endocarditis, some of the strains used by him were obtained from the alimentary canal of the normal human being. Since the publication of his work many others⁹ have reported the production of endocarditis in various animals. Vegetative endocarditis has followed these various procedures in a relatively small percentage of experimental animals. Kinsella^{9c} claimed to have obtained endocarditis in the majority of his animals by damaging the valve first.

A FACTORS AFFECTING THE GROWTH OF *STR. VIRIDANS* IN VITRO

1 *The Behavior of Str. Viridans in Fibrin*—The first step in the present study was to follow the growth of *Str. viridans* in fibrin, the medium in which the organism grows in man.

For this purpose fibrin was collected from sterile specimens of dog blood and cut into approximately 3 or 4 mm cubes. Fifteen of these cubes were inoculated with 0.5 cc of a twenty-four hour broth culture of *Str. viridans* obtained originally

5 (a) Wright, H. D. *J. Path. & Bact.* **29** 5, 1926. (b) Kinsella, R. A., and Hayes, C. M. *Proc. Soc. Exper. Biol. & Med.* **24** 887, 1927.

6 Harbitz, I. *Deutsche med. Wchnschr.* **25** 121, 1899.

7 Ribbert, J. *Deutsche med. Wchnschr.* **11** 717, 1885.

8 Rosenbach, O. *Virchows Arch. f. path. Anat.* **105** 215, 1886.

9 (a) Rosenow, E. C. *J. Infect. Dis.* **7** 411, 1910. (b) Detweiler, H. K., and Robinson, W. L. *Experimental Endocarditis*, *J. A. M. A.* **67** 1653 (Dec. 2) 1916. (c) Kinsella, R. A. *Proc. Soc. Exper. Biol. & Med.* **20** 252, 1923. (d) Wright^{5a}

from the blood of a patient with subacute bacterial endocarditis. They were then incubated for forty-eight hours in normal dextrose broth, and at the end of this time each cube of fibrin was placed in 5 cc of physiologic solution of sodium chloride. At the same time, for control purposes, tubes containing 5 cc of physiologic solution of sodium chloride and tubes containing 5 cc of normal dextrose broth were inoculated with 0.5 cc of a twenty-four hour broth culture of the same organism. In order to determine the period of growth of the organism, one of the cubes was removed from the original saline solution every third day and placed in normal dextrose broth for subculture, and subcultures of the controls in physiologic solution of sodium chloride and in dextrose broth were also made every day on blood agar plates.

The results summarized in table 1 show clearly that fibrin offers an ideal medium for the continued viability of *Str. viridans*, growth being obtained on subculture even after forty days. In contrast, the culture in dextrose broth became sterile in six days and that in saline solution in two days.

2 *The Behavior of Str. Viridans in Pure Serum*—Since *Str. viridans* growing in the fibrin of valvular vegetation is exposed to the plasma

TABLE 1—Data on Cultures

Material Infected with <i>Str. Viridans</i>	Number of Days Before Subcultures Were Sterile
Fibrin mass	Over 40
Physiologic solution of sodium chloride	2
Dextrose broth	6

of the circulating blood, it is conceivable that in vivo the presence of certain immune bodies in the plasma might determine the growth and survival of the organism. Accordingly, it was thought essential to determine in vitro the effect of serums from various sources on the growth of this bacterium.

For this purpose blood was obtained from four sources: (a) from normal adults, (b) from patients with subacute bacterial endocarditis, (c) from normal dogs and (d) from dogs specifically immunized against the strain of *Str. viridans* used. The immune dog serum was prepared as follows. Dogs were given injections of 1 cc of twenty-four hour broth culture of *Str. viridans* intravenously every other day for not less than a month, and the presence of immunity was judged by the agglutinin and opsonin reactions of the blood.

In the majority of instances the serum was prepared by defibrination with glass beads. In a few instances plasma was used, minimal amounts of citrate having been added to prevent clotting. After centrifugation the serum was drawn off with a pipet. One loopful of twenty-four hour broth culture of *Str. viridans* was added to each 5 to 10 cc sample. The average number of bacteria thus inoculated as determined by colony count, was 4,000,000. Growth was determined in all instances by subcultures made on blood agar plates at the end of twenty-four and forty-eight hours. Three strains of *Str. viridans* were used, each obtained from cultures of blood of different patients with subacute bacterial endocarditis. In two

cases the serum was taken from a patient with subacute bacterial endocarditis, and the strain of organism added was the one isolated from that patient

The results summarized in table 2 show that in thirty-four of the thirty-five serums used the streptococci were able to survive for at least forty-eight hours. In fact, it was found that all twenty serums which were subcultured longer than forty-eight hours showed growth continuing for from three to ten days. No gross difference was observed in the growth of the organism in the serums of different origin. In fact, the organism grew as well in serums which contained immune bodies (the agglutination titer of each of the four dogs was over 640) as in those in which there were no immune bodies.

TABLE 2—Data on Serums

Sources of Serums	Number of Different Samples	Number Showing Growth in 24 Hr	Number Showing Growth in 48 Hr
Normal man	8	7	7
Patient with subacute bacterial endocarditis	4	4	4
Normal dog	19	19	19
Immunized dog	4	4	4

TABLE 3—Bacterial Counts

	Bacteria Added per 5 Cc	Bacteria per 5 Cc in 24 Hr	Bacteria per 5 Cc in 48 Hr
Serum 1	1,200,000	2,400,000	
Serum 2	1,200,000	1,800,000	
Serum 3	1,200,000	2,100,000	
Serum 4	1,200,000	2,808,000	
Serum 5	2,020,000	3,460,000	38,000,000
Serum 6	2,020,000	4,020,000	32,000,000
Broth	2,020,000	8,000,000,000	

Our results indicate that serum is a medium that is suitable for survival of the organism. However, actual colony counts showed that growth is less luxuriant in serum than in broth (table 3).

3 *The Behavior of St. Viridans in Suspensions of Serum Containing White and Serum Containing Red Blood Cells*.—Preliminary experiments showed that the growth of *St. viridans* is irregular in whole blood, unlike the growth in serum. It appears therefore that the formed elements in the blood might be directly or indirectly responsible for the inhibition of bacterial growth. This was tested experimentally by observing the fate of cultures of *St. viridans* in serum containing suspensions of either white or red blood cells.

For this purpose defibrinated whole blood was obtained from five normal dogs. The sample of blood from each dog was centrifugated at high speed for one hour. At the end of this time the serum, the leukocytic cream and the portion of red blood

cells were separated by pipetting. Then the white blood cells and red blood cells were separately resuspended in from 5 to 10 cc of serum obtained from the same dog. A loopful of twenty-four hour broth culture of *Str viridans* was added to each of the five tubes containing a pure suspension of white blood cells and to each of the five tubes containing a pure suspension of red blood cells. All ten tubes were placed in a mechanical shaker for sixty minutes to insure sufficient contact between the formed elements of the blood and the bacteria, since otherwise the cells tend to settle to the bottom of the test tube and do not remain in contact with the bacteria. After sixty minutes of agitation subcultures were made immediately on blood agar. The original suspensions were incubated, and subcultures were made again after twenty-four and after forty-eight hours.

The results shown in table 4 clearly indicate that a suspension of white blood cells is an effective and rapid bactericidal agent. The bactericidal action was such that four of five cultures suspended in white blood cells plus serum became sterile in an hour, whereas all five cultures suspended in red blood cells plus serum showed growth for at least forty-eight hours.

TABLE 4—Data on Growth in Serum

Suspension	Number of Different Samples	Growth in 60 Min	Growth in 24 Hr	Growth in 48 Hr
Red blood cells plus serum	5	5	5	5
White blood cells plus serum	5	1	1	1

4 *The Behavior of Str Viridans in Whole Blood in Vitro*—The bactericidal action of white blood cells suspended in serum led us to determine whether or not the bactericidal power was retained by the white blood cells in their natural environment—the blood.

This was tested with specimens of whole blood obtained from the four sources used in the experiments with pure serum. Approximately 10 cc of defibrinated whole blood was used in each case, and one loopful of twenty-four hour broth culture of *Str viridans* was added to each. The average number of bacteria contained in this loopful was by colony count approximately 4,000,000. All tubes, including those containing the control serum, were placed in the mechanical shaker for sixty minutes. All the samples were then immediately subcultured on blood agar, incubated and subcultured again after twenty-four and after forty-eight hours.

The results obtained with whole blood (table 5) were similar to those obtained with pure suspensions of white blood cells in serum (table 4), in that agitation for an hour was found to cause the rapid destruction of bacteria. No gross difference could be observed between the various types of whole blood used provided only the culture was shaken for an hour. The whole blood of the patient suffering from subacute bacterial endocarditis destroyed *Str viridans* as efficiently as the whole blood of the specifically immunized dog.

B FACTORS AFFECTING THE GROWTH OF STR VIRIDANS IN VIVO

1 *The Behavior of Str Viridans in the Blood Stream of the Dog*—

While experiments in vitro indicated that whole blood when agitated has a marked and rapid bactericidal effect on Str viridans, it seemed important to attempt to quantitate this bactericidal effect in the blood stream of the living normal dog

For this purpose Str viridans was injected into four normal dogs, and the actual number of bacteria per cubic centimeter of blood was determined every hour for three hours and then twenty-four, forty-eight and seventy-two hours after the injection

TABLE 5—*Data on Growth in Whole Blood in Vitro*

Medium	Number of Different Samples	Growth in 1 Hr	Growth in 24 Hr	Growth in 48 Hr
Normal whole blood of human adult	9	2	2	2
Normal serum of human adult	9	8	8	8
Whole blood from patients with subacute endocarditis	4*	1	1	1
Serum from patients with subacute endocarditis	4*	4	4	4
Immunized dog whole blood	3	None	None	None
Immunized dog serum	3	2	2	2

* In two of these samples the streptococci that were added were taken from the blood stream of the patient whose blood serum was used as the medium

TABLE 6—*Bacterial Counts for Experiments Made in Vivo*

	Dog 1 1,000,000	Dog 2 1,500,000	Dog 3 1,000,000	Dog 4 3,000,000
Number of bacteria given per cc of blood				
Number of bacteria counted per cc				
After 1 hr	53	1,200	24	20
After 2 hr	12	1	2	1
After 3 hr	2	0	0	0
After 24 hr	3	0	0	0
After 48 hr	3	0	0	0
After 72 hr	0	0	0	0

The results summarized in table 6 indicate that in three of the four dogs the circulating blood was completely sterilized in two hours and that in the fourth dog the bacterial content was markedly reduced in this period, although two days was required for the blood stream to become completely sterile. Unlike the destruction in vitro of Str viridans by shaken whole blood or by serum plus white blood cells, the sterilization of the blood stream of the living dog may be due to factors other than those present in the circulating blood stream itself such as the bacterial deposit in various tissues and the destruction of bacteria by the fixed phagocytic cells of the body. However, since dog blood in vitro showed a similar rapid bactericidal power, it appears likely that the sterilizing factors in the living dog are essentially the same as in the test tube experiments

In all these experiments the action of the white blood cells was studied in a medium containing blood serum or plasma, as it is difficult to conceive of white blood cells in the living animal completely isolated from blood plasma. Nevertheless our results show that destruction of these bacteria does not occur to any measurable extent in the absence of white blood cells. In essence, our results support the view of Metchnikoff concerning the primary importance of the white blood cell. A rough computation indicates that on the basis of these animal experiments the average man could easily dispose of more than 1,000,000,000 bacteria of this variety per hour.

2 *The Production of Str Viridans Infection in the Circulatory System of the Normal Dog*—I *Aorta*. The results obtained on the bactericidal action of blood in the experiments made in vitro and in vivo suggested the possibility that infection with *Str viridans* might be produced in a dog if the organisms could be shielded physiologically from the white blood cells. This, we felt, might be accomplished by inserting a capsule containing a blood agar focus of *Str viridans* into the blood stream and permitting it to float free in the stream, attached by a thread to a single part of the wall of the vessel. White blood cells would penetrate the capsule only in small numbers, because of the momentum of the rapidly flowing blood current but fibrin might become attached to this foreign body and serve as a medium for the continued proliferation of the bacteria. After numerous trials the following technic was developed.

A small hollow bakelite capsule (measuring approximately 7 by 3 mm), open at one end, was used. The wall of the capsule was 0.5 mm thick and besides the opening at the end had about sixteen small perforations (0.5 mm in diameter) elsewhere which permitted contact between the contents of the capsule and the circulating blood. After the capsule was filled with blood agar culture the open end was partially closed with a four-ply suture, which effectively kept the solid agar in situ. A perforation in the solid end of the capsule was made for the thread which held the capsule in place. Throughout this paper a capsule of this type will be called an infected capsule.

The infected capsule was inserted into the abdominal aorta just below the renal arteries. The thread attached to the capsule was fastened into the aortic wall, enabling the capsule to float freely in the blood stream but preventing it from being carried away from the site of its insertion. At the same time the contact of the capsule with the wall of the aorta itself was minimal. In seven normal dogs an infected capsule was inserted in this way into the aorta by a transperitoneal approach with aseptic precautions and with the use of an anesthetic. The developments after operation were followed, and blood cultures were made every third day. Autopsy was performed in each case and histologic sections of the covering of the capsule (if present) and its environment were studied.

The results summarized in table 7 reveal that only two of the dogs had capsules covered with fibrin, in the remainder the capsule either was lying free in the aorta without a covering of fibrin or was

embedded in granulation tissue originating from the aortic wall. When granulation tissue enclosed the capsule and white blood cells invaded it, no streptococci could be demonstrated (dogs 5 and 7). The continuation of bacterial growth occurred only in the absence of invasion by granulation tissue and white blood cells (dogs 1 and 3) and the most luxuriant growth occurred when the capsule had a heavy covering of fibrin (figs 1 and 2). While organisms could be demonstrated post mortem in the capsule in dog 6, the growth was so scanty that the organisms shed into the blood stream were too few to give positive blood cultures. The findings for dog 7 are interesting. Here apparently up to about the

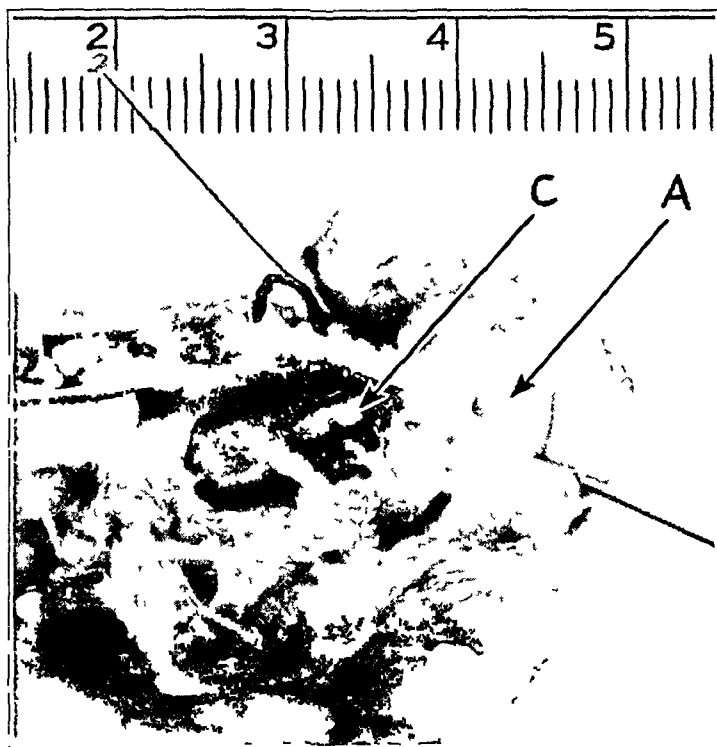


Fig 1—The gross appearance of a capsule (C) covered by fibrin after remaining within the aortic lumen (A) of dog 3 for ten days

tenth day the growth in the capsule was sufficiently extensive to give positive blood cultures, but after this the blood cultures became sterile, presumably because of the ingrowth of granulation tissue and white blood cells, as demonstrated post mortem. This ingrowth between the tenth and the twenty-second day was sufficient to sterilize the capsule as shown post mortem by the absence of organisms (fig 3).

II Cardiac Cavity The foregoing experiments were repeated except that the infected capsule was inserted directly into the cardiac cavity instead of into the aorta.

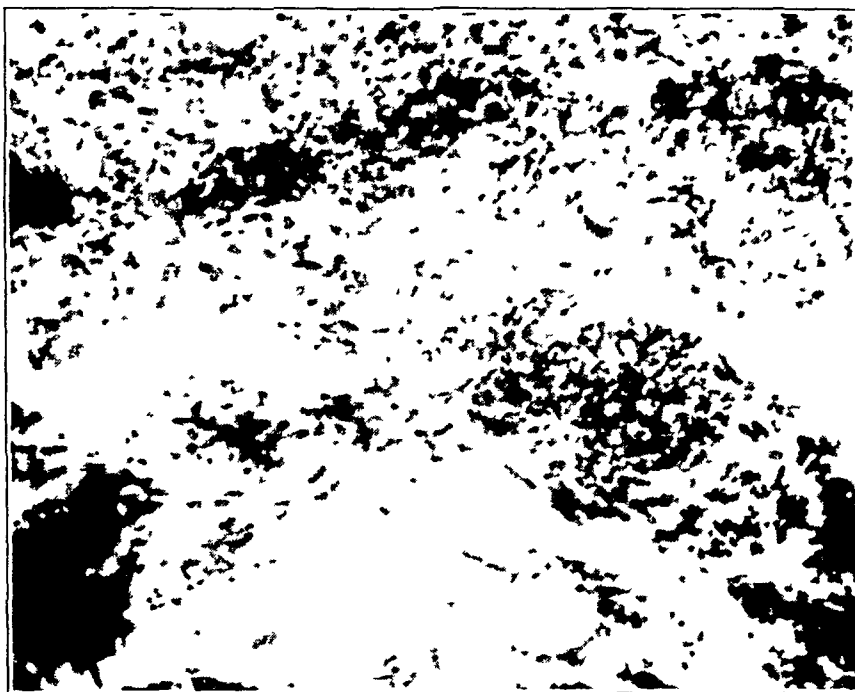


Fig 2—A microscopic section of the fibrin surrounding the capsule shown in figure 1. Observe the myriad of cocci, with the absence of white blood cells. Gram-Weigert stain, $\times 960$.

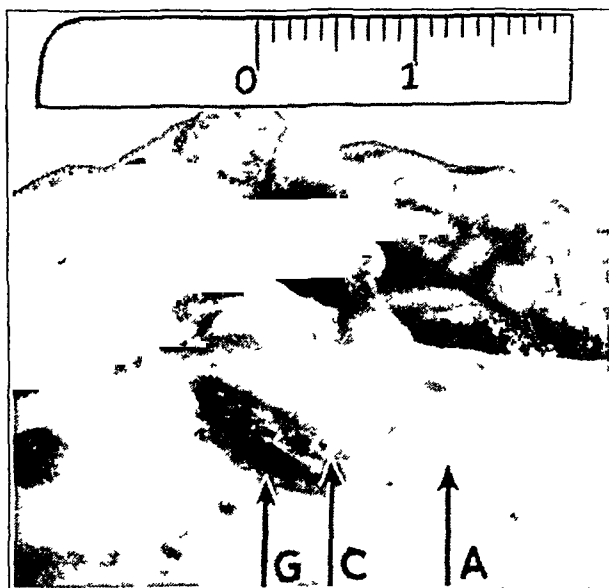


Fig 3—The gross appearance of a capsule (C) which became attached to the aortic wall after remaining in the aortic lumen of dog 7 for twenty-two days. Note the absence of fibrin, the granulation tissue (G) growing from the aortic wall and the smooth lining of the aorta (A). No organisms were present in this capsule.

A series of thirteen dogs was used. The infected capsules (from one to three) were inserted with aseptic precautions directly into the cardiac cavity. For this purpose a long, pointed hollow steel trocar, 20 cm in length and 3.5 mm in diameter, was employed. The infected capsule was placed in the hollow tube, and a steel plunger (22 cm in length and 1.5 mm in diameter) was used to push the capsule half way down the trocar. One end of the 36 cm of thread attached to the capsule was kept outside the trocar. After the trocar had been prepared in this way, the dog was anesthetized, and an incision was made in the fourth intercostal space 4 cm lateral to the left sternal margin. The trocar was inserted through this opening until the thrust of the heart was felt against it. A quick stab was then made, and entrance into the cardiac cavity was indicated by the spurting of blood past the capsule and the plunger. When blood appeared the plunger was quickly thrust in, forcing the capsule into the cardiac cavity, the plunger was then carefully withdrawn and the trocar quickly removed. The end of thread holding the capsule in place was then sewed loosely under the skin. Thus, the capsule was

TABLE 7—Results Obtained After Inserting an Infected Capsule into the Aorta

Dog No	Duration of Life, Days	Positive Blood Cultures	Cause of Death	Autopsy Observations			
				Fibrin Around Capsule	Granulation Tissue Around Capsule	Large Number of White Cells in Capsule or Fibrin	Diplococci in Capsule or Fibrin
1	5	3d and 5th days	Rupture of aorta	Present	Absent	Absent	Present
2	7	None	Peritonitis	Absent	Absent	Absent	Absent
3	10	5th and 8th days	Killed	Present	Absent	Absent	Present
4	14	8th, 11th and 14th days	Intestinal obstruction	(Incomplete autopsy)			
5	15	None	Killed	Absent	Present	Present	Absent
6	16	None	Killed	Absent	Absent	Absent	Present
7	22	6th and 10th days	Killed	Absent	Present	Present	Absent

free in the cardiac cavity and at least temporarily unattached to the endocardial lining, and yet it was prevented by the restraining thread from leaving the cardiac chamber. With experience the procedure can be carried out quickly and without too much loss of blood. Occasionally, when a coronary artery was injured or when more than one opening was made in the ventricular wall, death resulted from acute pericardial tamponade.

The results in the successful experiments are summarized in table 8. The data in this table show that every animal which survived longer than two days gave a positive blood culture after the second day. This is contrary to the findings obtained by us when a single massive dose of the organism was injected into the blood stream of the dog. None of the dogs died of the *Str. viridans* infection directly but of some complication.¹⁰ Figures 4 to 7 show the gross appearance of the capsules

10 Several dogs succumbed to septicemia due to a mixed infection, a gram-positive rod-shaped anaerobic bacillus being found in the capsule in addition to the streptococcus. This bacillus, which we have found to be a common secondary invader in the dog, was not present when the infected capsule was inserted.

TABLE 8—Results Obtained After Insertion of One or More Infected Capsules into the Cardiac Cavity

Dog No.	Number of Infected Capsules	Duration of Life, Days	Positive Blood Cultures	Cause of Death	Autopsy Observations						V alves of Heart Affected	Other Observations
					Location of Capsule	Fibrin Around Capsule	Granulation Tissue Around Capsule	Number of White Cells in Capsule or Fibrin	Diplococci in Capsule or Fibrin	Valves of Heart Affected		
8	1	1	No cultures taken	Killed	Cardiac cavity	Present (thrombus)	Absent	Absent	Present	None	None	
9	1	1	No cultures taken	Pneumonia	Cardiac cavity	Absent	Absent	Absent	Present	None	None	Extensive pneumonia
10	2	2	No cultures taken	Pneumonia	Cardiac cavity	Present	Absent	Absent	Present	None	None	Extensive pneumonia
11	2	4	3d day	Cerebral embolism	Cardiac cavity	Present	Absent	Absent	Present	None	None	Cerebral embolus
12	1	6	3d day	Killed	Cardiac cavity	Present	Absent	Absent	Present	None	None	Infarct in left kidney
13	2	7	3d day	Pneumonia	(a) Cardiac cavity (b) Pericardial sac	Present Absent*	Absent Present*	Absent Present*	Present Absent*	Vegetation on tricuspid valve containing diplococci	None	Pneumonia
14	3	8	3d, 4th and 8th days	Septicemia	Cardiac cavity	Present	Absent	Absent	Present (rod shaped bacilli also present)	None	None	Multiple granulomatous areas in kidneys, spleen and lung containing diplococci and rod shaped organisms
15	3	11	3d and 10th days	Septicemia	Cardiac cavity	Present	Absent	Absent	Present (rod shaped bacilli also present)	None	None	Same as for dog 14
16	2	23	3d, 5th and 20th days	Killed	Cardiac cavity	Present	Absent	Absent	Present	None	None	Infarct in left kidney
17	1	9	3d day	Septicemia	Cardiac cavity, attached to mitral valve	Present	Absent	Absent	Present	Vegetation on mitral valve containing diplococci and rod shaped bacilli	None	Same as for dog 14
18	1	52	20th day	Killed	Myocardium, extending into cardiac cavity	Absent*	Present*	Present*	Absent*	None	None	Two healed infarcts in left kidney
19	3	8	3d and 6th	Killed	(a) Cardiac cavity, attached to aortic valve (b) Pericardial sac (c) Myocardium	Present	Absent	Absent	Present	Vegetation on aortic valve containing diplococci	None	
20	3	14	3d, 6th, 9th and 12th days	Septicemia	Not found, ligatures present in cardiac cavity	Absent*	Present*	Present*	Absent*	Vegetations on aortic and mitral valves containing diplococci in chains and rod shaped bacilli also present in vegetation on mural endocardium of left ventricle	None	Multiple fresh infarcts in both kidneys

* Sites other than the cardiac cavity



Fig 4—The appearance of a capsule covered by a thrombus after one day in the left ventricular cavity of dog 8. The capsule is completely surrounded by thrombus and lies under the chordae tendineae of the mitral valve.



Fig 5—The appearance of two capsules covered by fibrin after four days in the left ventricular cavity of dog 11. One capsule is seen to be embedded in the mural endocardium beneath the chordae tendineae of the mitral valve, the other is free in the cavity of the heart.



Fig 6—The gross appearance of a capsule covered by fibrin (indicated by arrow) after six days in the left ventricular cavity of dog 12. The capsule is completely surrounded by fibrin.



Fig 7—The appearance of two capsules covered by fibrin (indicated by arrows) after twenty-eight days in the left ventricular cavity of dog 16. Observe the thickening of the chordae tendineae and the presence of mural involvement. The capsules are free in the cavity of the heart.

covered with fibrin and thrombus in the hearts of four animals, dogs 8, 11, 12 and 16, respectively. These are typical of the rest, except that in dog 9 the capsule remained free in the cavity for one day without deposition of fibrin.

Figures 4 to 7 show that the amount of the deposit of fibrin was not always related to the duration of time. The fibrin covering the capsule after four days was almost as extensive as that covering the capsule after twenty-eight days (compare figs 5 and 7). This is further borne out by the one day old capsule (fig 4) which had evoked a thrombus with a greater deposit of fibrin than that caused by many of the other capsules, despite its short residence in the heart. The size of the deposit of fibrin appearing on the mural endocardium, however, seemed to depend on the length of time the capsule was in place. Histologically,

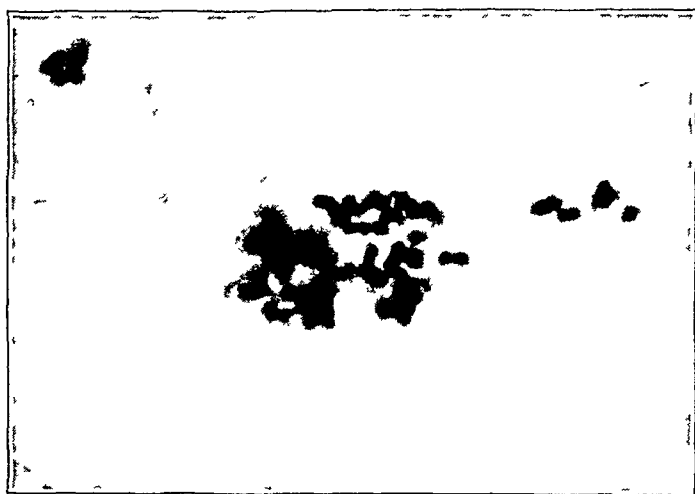


Fig 8—The microscopic appearance of fibrin covering a capsule which had been in the left ventricular cavity of dog 16 for twenty-eight days. A colony of diplococci can be seen. Notice the scarcity of polymorphonuclear leukocytes. Gram-Weigert stain, $\times 1,300$.

the fibrin covering the free-floating capsule showed occasional white blood cells, an occasional accumulation of red blood cells and, diffusely spread through the fibrin, gram-positive diplococci. Figure 8 shows the typical microscopic appearance of the fibrin covering a capsule within the cardiac cavity (dog 16).

The experience with infected capsules in the cardiac cavity is in accord with that with infected capsules in the aorta. Fibrin formation, however, was greater in the heart than in the aorta, probably because in the heart more eddies are present and the flow is intermittent. This apparently also accounts for the greater certainty of development of infection in the latter site.

3 *Comparison of the Reaction of the Cardiac Valves to Str. Viridans with That of Other Tissues*—Three of the dogs in the preceding series showed infected vegetations produced by contact with an infected capsule, one on the tricuspid (dog 13), one on the mitral (dog 17) and one on the aortic valve (dog 19). Furthermore in the course of some



Fig 9—The microscopic appearance of a valvular vegetation produced by repeated intravenous inoculation of *Str. viridans* into dog 21. Note the relative paucity of polymorphonuclear cells in the fibrocytic proliferating tissue of the valve underlying the vegetation and the large densely stained masses composed of bacteria in the vegetation and valvular fringe. Hematoxylin and eosin stain, $\times 560$.

experiments in which an attempt was made to infect sterile capsules inserted in the blood stream by repeating massive intravenous injections

of *Str viridans* (two or three injections of 500 000,000 bacteria per week for a month), two of the three animals showed an infected vegetation on one of the cusps of the aortic valve (dogs 21 and 22)¹¹

All these vegetations, regardless of origin, on histologic examination were shown to consist of fibrin, colonies of diplococci and scattered white and red blood cells. The substance of the valve itself directly beneath the vegetation showed a proliferative reaction, but the striking feature was the desultory and indifferent polymorphonuclear response. The polymorphonuclear leukocytes scattered in the vegetation bore no apparent relation to the bacterial colonies and appeared to have been

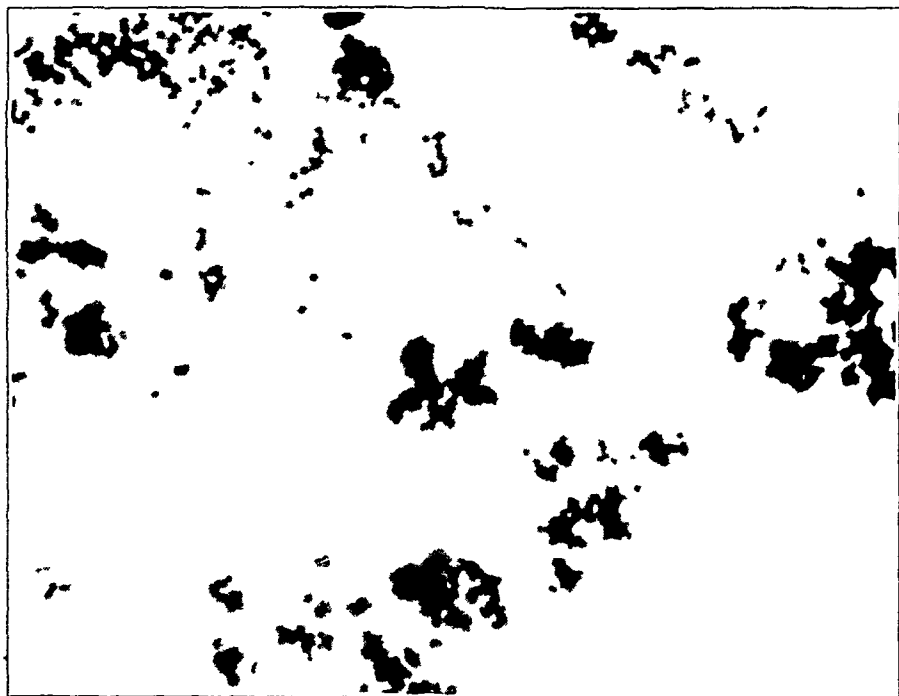


Fig 10—The microscopic appearance of a vegetation produced by intravenous inoculation of *Str viridans* into dog 22. Note the absence of polymorphonuclear leukocytes in the fibrin meshes and the presence of bacterial chains and clumps. Gram-Weigert stain, $\times 960$.

caught as the fibrin was deposited. The typical illustrations shown in figures 9 and 10 indicate clearly the paucity of polymorphonuclear leukocytes both in the valvular base and in the fibrin vegetations. The results indicate that the valves of the heart do not respond to *Str viridans* infection with an inflammation characterized by an accumulation of polymorphonuclear leukocytes but show predominantly a proliferative endothelial leukocytic reaction.

11 This procedure, however, failed to infect the sterile capsules.

In the course of these experiments data were obtained on the reaction of other tissues to an infected focus. In two animals into which more than one infected capsule was introduced contact was made not only with a cusp of a valve but at the same time with other structures. Thus, in dog 13, in which an infected capsule became adherent to the

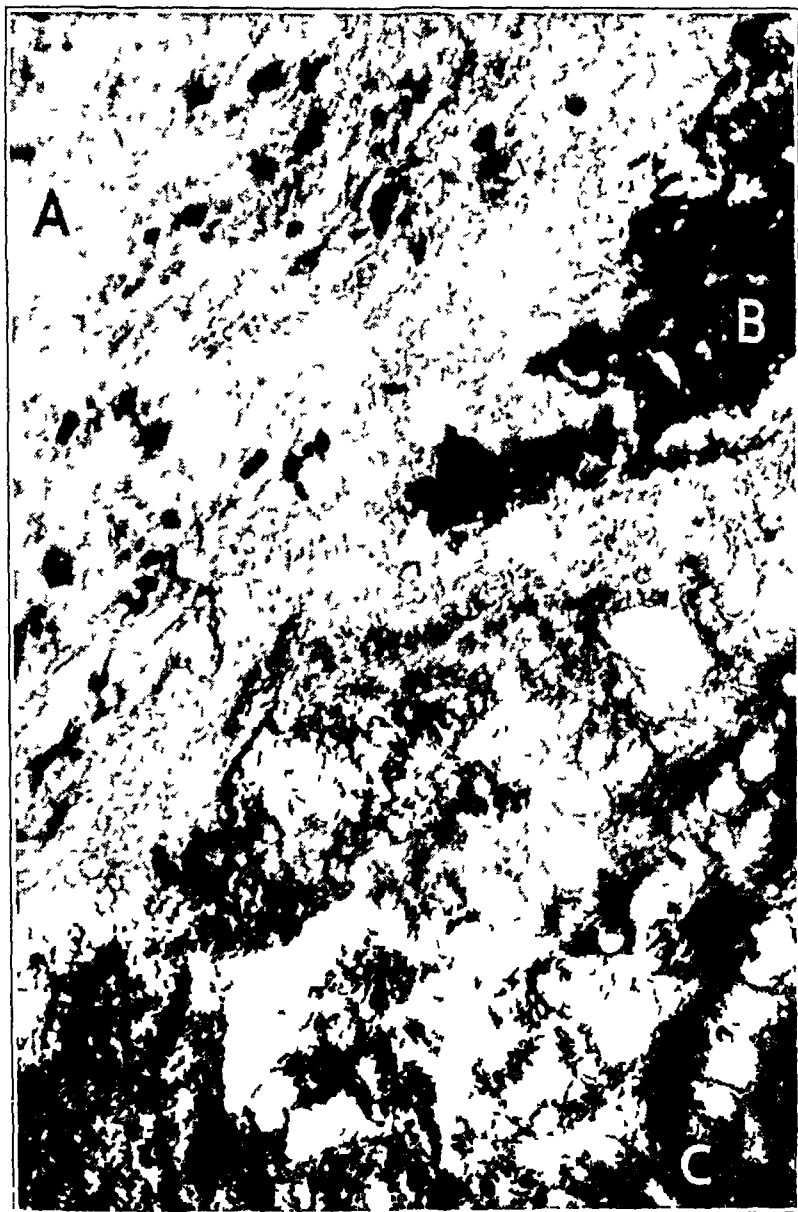


Fig. 11—The microscopic appearance of the valvular substance (C) underlying an infected vegetation (A) produced by infected capsular contact in dog 19. Note the dense masses of bacteria (B) and the relative absence of polymorphonuclear leukocytes, both in the vegetation itself and in the valvular substance immediately adjacent to the vegetation. Hematoxylin and eosin stain, $\times 660$.

tricuspid valve, causing the development of vegetation, a second infected capsule became attached to the pericardium. In dog 19, in which an infected capsule that was lodged in the sinus of Valsalva became adherent

to the corresponding aortic cusp and caused the growth of vegetation, a second infected capsule became attached to the pericardium, and a third infected capsule, to the inner wall of the left ventricle (in contact with the myocardium and the endocardium) There was a striking contrast between the fate of the capsule attached to the valve and that of the capsule in the other localities

In dog 13 the polymorphonuclear reaction in the valvular base of the vegetation was negligible, although there was some endothelial leukocytic proliferation The vegetations themselves contained few polymorphonuclear cells, and those that were present were not in the neighborhood of the bacterial colonies In contrast with this valvular reaction, the infected capsule in the pericardium of this dog caused an intense

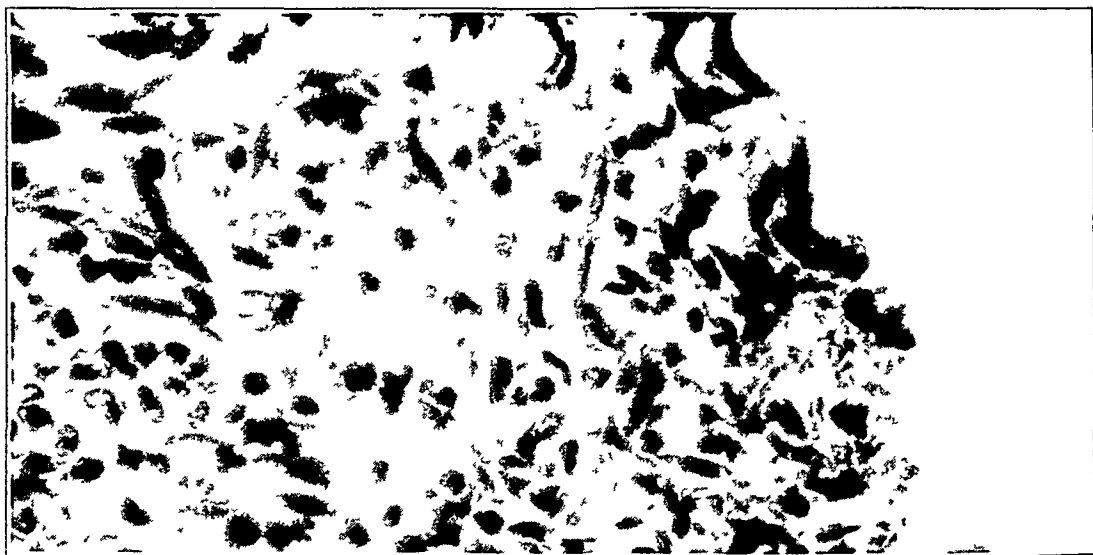


Fig 12—The microscopic appearance of a section of the myocardium of dog 19 immediately underlying a second infected capsule Note the marked accumulation of polymorphonuclear leukocytes in this area and the many fibroblasts Hematoxylin and eosin stain, $\times 660$

polymorphonuclear reaction, with fibroblastic proliferation and the formation of new blood vessels, and it was obvious that the lesion was being walled off and healed

In dog 19, while the valvular lesion showed the typical reaction, as just described (fig 11), both the capsule in the myocardium and that in the pericardium evoked a tremendous accumulation of polymorphonuclear leukocytes and fibroblasts and the formation of new blood vessels It was obvious that healing was taking place in these capsules (figs 12 and 13)

This type of reaction was not evoked by sterile capsules For example, in dog 24 a sterile capsule which was placed in contact with the

inner wall of the left ventricle elicited mainly a fibroblastic reaction (fig 14)

The occurrence of a reaction in the myocardium in the presence of an infected capsule suggested that complete healing probably would have taken place in this region. This impression was confirmed by further experiments. An infected capsule was inserted into each of five dogs (dogs 25 to 29) so as to be completely surrounded by myocardial tissue. Blood cultures were made every third day, and the animals were killed sometime between the ninth and the eighteenth day after insertion of the capsule. None of these dogs gave a positive blood culture,

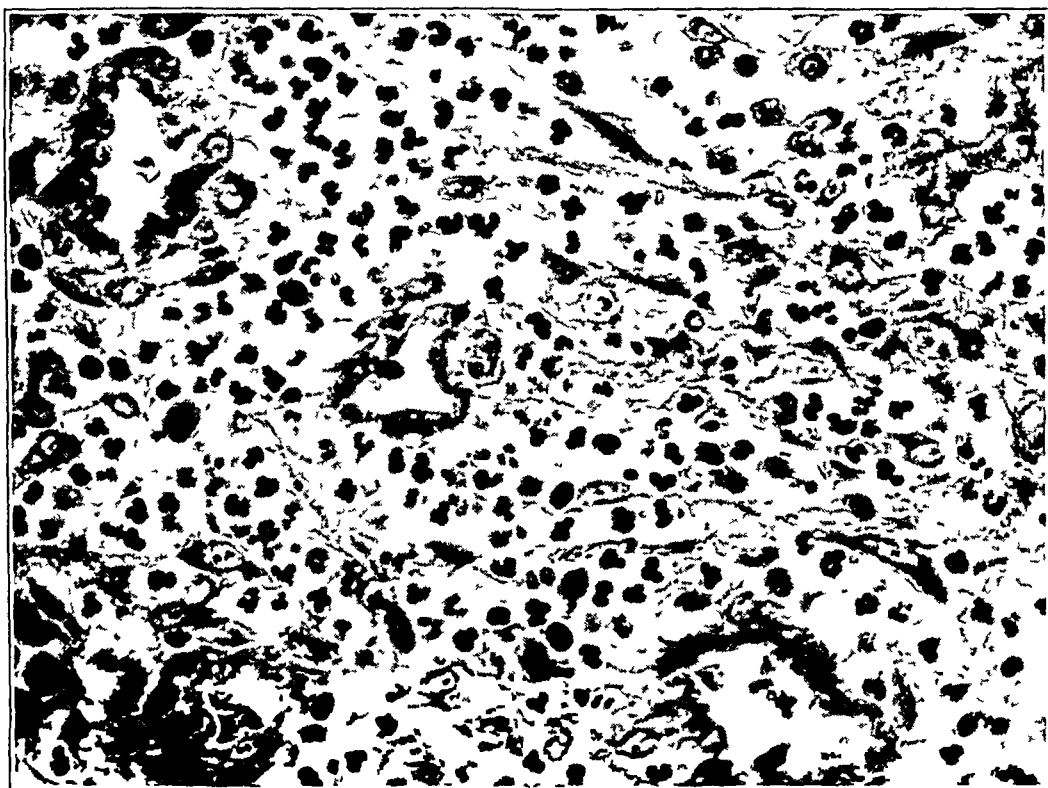


Fig 13—The microscopic appearance of a section of the pericardium of dog 19 surrounding a third infected capsule. Note the tremendous accumulation of polymorphonuclear leukocytes and fibroblasts and the concomitant formation of new blood vessels. Hematoxylin and eosin stain, $\times 560$

and none showed the slightest ill effect. At autopsy each capsule was covered by a firm sheath of tissue, which separated it from the healthy-appearing muscle tissue. There was no indication of spread of the infection in any of these animals. The histologic examination of the youngest capsular insertion (nine days old) revealed many polymorphonuclear leukocytes within it and a fibroblastic wall forming around it to wall it off (fig 15). Examination of the oldest capsular insertion (eighteen days) revealed considerably fewer polymorphonuclear cells but a more extensive and denser-appearing fibroblastic encapsulation,

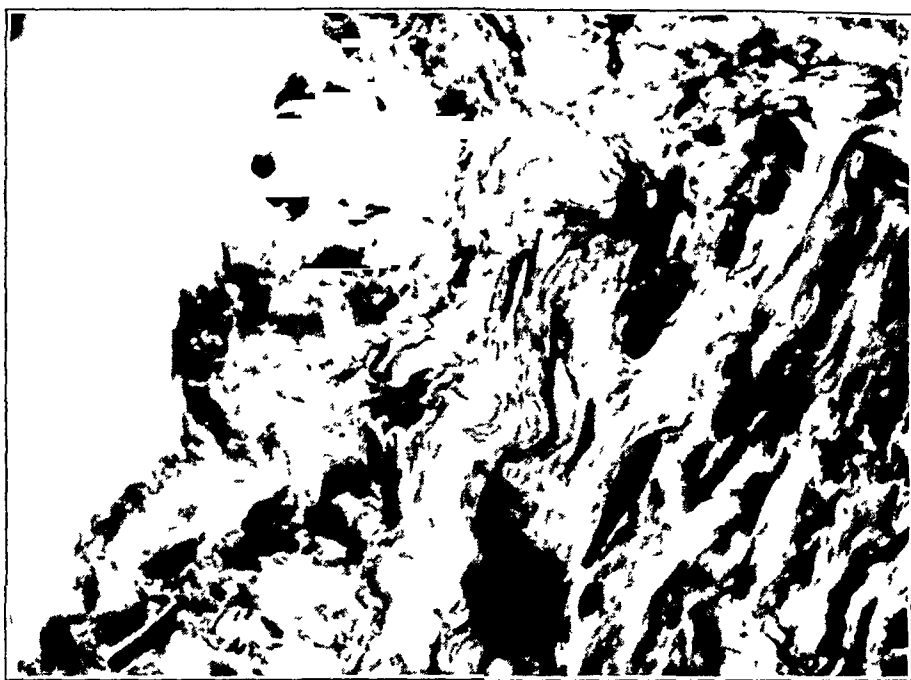


Fig 14—The microscopic appearance of a section of the myocardium of dog 24, which had a sterile capsule in the same position as in dog 19 (fig 12) Hematoxylin and eosin stain, $\times 660$

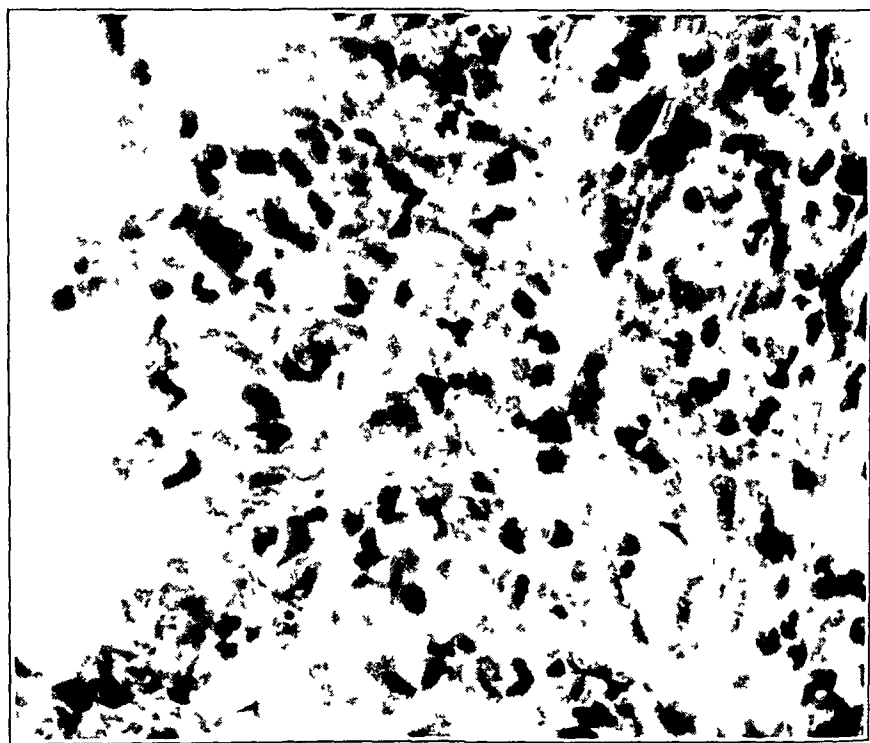


Fig 15—The microscopic appearance of the myocardial response to an infected capsule after nine days within the myocardium of dog 25. Note the accumulation of polymorphonuclear leukocytes, the formation of new blood vessels and the ingrowth of fibroblasts. Hematoxylin and eosin stain $\times 660$

with no organisms observed within the area enclosed. The other animals showed pictures intermediate between these two. It is clear that the infected capsule introduced into the cardiac muscle was walled off and rendered sterile.

Similar sterilization and leukocytic infiltration occurred within twenty-four hours after the injection of *Sti viridans* subcutaneously into another dog, this was demonstrated by biopsy. The reaction of the pleura to an infected capsule in one animal examined post mortem was similar to that observed in the pericardium. Sterile capsules inserted into the pleura were observed post mortem to have caused only a fibroblastic reaction such as that noted when a sterile capsule had been placed within the myocardium.

COMMENT ON RESULTS

Our results show that 1. *Sti viridans* can grow in blood that is free from white blood cells. 2. This growth is particularly persistent on fibrin. 3. When white blood cells in serum are brought in contact with the organisms and kept there by continued agitation the culture is sterilized.

A rough calculation on the assumption that human blood acts quantitatively *in vivo* as it does *in vitro*, indicates that in the patient with *Sti viridans* infection the blood stream can be cleared of organisms at the rate of 1 000 000 000 per hour. In this connection it is interesting to note that positive blood cultures were obtained constantly by Hamman and Rienhoff¹² for a patient with subacute infection with *Sti viridans* located on a femoral arteriovenous aneurysm, each culture giving from twenty to fifty colonies per cubic centimeter of blood. However, the blood culture made two hours after the infected focus was removed was sterile, and cultures on six successive days also were sterile. The time of disappearance in this case is of the order found in our experiments on dogs to which huge doses of *Sti viridans* were given.

Our results show that the organism will grow *in vitro* in serum obtained from normal adults, from patients with subacute bacterial endocarditis, from normal dogs and from dogs immunized to the strain of *Sti viridans*. No detectable gross difference could be demonstrated in the growth in the various serums. The immune properties of the blood serum therefore play a much less important role in the destruction of this bacterium than is commonly accepted. This is supported by the fact that no gross difference could be demonstrated *in vitro* in the sterilizing action of agitated whole blood from the same four sources.

¹² Hamman, L., and Rienhoff, W. J., Jr. Bull. Johns Hopkins Hosp. 57: 219, 1935.

Our results show that a focus infected with *Str viridans* will grow *in vivo* in the blood stream of the normal dog, provided it is protected from the action of white blood cells. Under these circumstances bacteremia is started which will last for several weeks or more. With the deposition of fibrin around the focus an active subacute infection with *Str viridans* can be established in a previously normal dog. The opportunity for the deposit of fibrin was found to be greater in a focus in the cardiac cavity than in one in the aortic blood stream. Other factors besides the time of residence determine the amount of fibrin deposited on the infected focus in the cardiac cavity. In time the foci in the cardiac cavity showed extension of the infection on to the chordae tendineae, mural endocardium and valves, apparently by contact. With the establishment of the focus in the cardiac cavity, some of the animals died of emboli or as the result of an overwhelming mixed septicemia.

In several animals vegetations were produced on the cardiac valves both by contact with the infected focus and by repeated massive intravenous injections of the organism. Infected foci were also placed in the myocardium, pericardium, pleura and aortic wall and subcutaneously some times in the same animal having an infected focus in the cardiac cavity or in a valve. In every instance the infection on the valve persisted, and in every instance the infection was sterilized in the other localities. The clue to the difference was observed on histologic examination to depend on a difference in tissue response to the infection on the valve and elsewhere in the body.

On the valve there was a dearth of leukocytes, and the reaction was proliferative, with few lymphocytes and only an occasional polymorphonuclear leukocyte. Consequently, the organisms were plentiful in the fibrin mesh. Even the portion of valve underlying the vegetation exhibited few polymorphonuclear leukocytes. In the vegetation the few leukocytes present were not close to the bacterial colonies but seemed to have been trapped as the fibrin mesh was laid down. The appearance of the valvular vegetation was like that of the fibrin-enclosed capsule within the blood stream. The fibrin in both localities acted to isolate the bacteria from the white blood cells of the blood stream, permitting them to grow and produce bacteremia.

In human beings the state of affairs reported both for the early lesion and for the fully developed vegetation is in accord with that noted by us in animals. Thus, Jaffe¹³ in his excellent description of the pathologic picture of early subacute endocarditis, emphasized that the early changes in the human valve infected with *Str viridans* are proliferative, the cells being proliferative, and that at first few, if any polymorphonuclear leukocytes are seen. Siegmund¹⁴ also has called atten-

13 Jaffe, R. H. *Virchows Arch f path Anat* **287** 379, 1932

14 Siegmund, H. *Virchows Arch f path Anat* **290** 3, 1933

tion to this proliferation of subendothelial cells following injury of the valve Harbitz⁶ and Wright,^{4b} in describing the fully developed vegetation caused by this organism, called attention to the fibrin mass, containing bacteria in abundance in the periphery, with only a few white blood cells in the same region.

In other sites than the valves or blood stream the reaction was observed to be different. The infected focus caused a marked tissue response, consisting of the formation of granulation tissue containing fibroblasts and newly formed blood vessels, which tended to wall off the focus, and, in addition, an abundant invasion of polymorphonuclear leukocytes.¹⁵ The result was destruction of the bacteria, sterilization of the focus and eventual healing and scar formation. Foci in these localities did not give positive blood cultures or signs of infection. This response to an infected capsule occurred in animals even when a second focus in the cardiac cavity or on the valve grew and established bacteremia and infection. Sterile capsules caused mainly a fibroblastic reaction.

It appears from these results that the response of the tissue in which the bacterium is deposited determines whether it will grow or be destroyed. On the basis of our work, the balance seems to depend on whether or not polymorphonuclear leukocytes invade the focus in large numbers. The deposition of fibrin acts as a barrier to white blood cells and as an excellent medium for bacterial growth. There is therefore no need to invoke the hypothesis that the infection persists because the organism acquires a resistance to the destructive elements in the blood or because the white blood cells lose their power to destroy the bacterium. The growth of *Str. viridans* is seemingly dependent on simple biologic and physiologic processes.

SUMMARY

Experiments *in vitro* established the fact that the strains of *Str. viridans* used in these experiments can grow in the serum (*a*) of normal adults, (*b*) of patients with subacute bacterial endocarditis, (*c*) of normal dogs and (*d*) of dogs specifically immunized against the particular strains used.

Experiments *in vitro* established the fact that *Str. viridans* can grow (*a*) in a serum suspension of red blood cells and (*b*) luxuriantly on fibrin.

Experiments *in vitro* established the fact that *Str. viridans* will not grow (*a*) in a serum suspension of white blood cells or (*b*) in practically

¹⁵ The presence of collections of polymorphonuclear leukocytes in the myocardium of patients with subacute bacterial endocarditis following coronary emboli has been reported by O. Saphir (Am J Path **11** 143 1935).

any sample of whole blood, regardless of source, provided constant protracted agitation is carried out (The sources of the samples of whole blood used were the same as those enumerated in the first paragraph of this summary)

It is concluded from our data that white blood cells plus serum are the effective agents in destroying *Sty viridans* in the blood stream. Animal experiments show that this is accomplished often within two hours and calculations indicate that on this basis human blood can destroy approximately 1,000,000,000 *Str viridans* per hour. Variation in the immunologic properties of the serum appear to play little part in this destruction.

A simple, rapid, consistent method of producing a focus of *Sty viridans* in the cardiac cavity experimentally is described. The production of infected vegetations on the leaflets of the cardiac valves is reported, and the fate of foci of *Str viridans* implanted in the aortic wall, myocardium, pericardium, pleura and subcutaneous tissue is described.

It is shown that the reaction of the valvular leaflet to *Sty viridans* is different from that of other tissues of the body. The early response of the valve is proliferative with little or no blood vessel or leukocytic invasion, fibrin is deposited on the vegetation, and bacterial growth flourishes in it. Elsewhere, except in some foci in the blood stream, typical granulation tissue surrounds the infected focus and walls it off. This is preceded by leukocytic invasion of the focus which sterilizes it. Healing takes place and eventually a scar is formed. When multiple foci of bacteria are introduced into one dog the sterilizing and healing reaction occurs at all sites except on the valve. At the same time that sterilization and healing occur in the other sites the focus on the valve enlarges by deposition of fibrin and infects the animal.

It is concluded that the sluggish inflammatory reaction of the valve is responsible for the early development of the infection.

It is concluded that the infection persists in the valve and in the capsule in the blood stream not only because the deposit of fibrin exceeds the invasion of white blood cells but because the fibrin offers an excellent medium for growth. No evidence was observed in these experiments that the bacterium acquires resistance to the action of white blood cells or that the latter lose their power to destroy the organism. Ultimately the fate of the infected focus seems to be determined by the balance of fibrin deposited and of granulation tissue ingrowth. The growth of *Str viridans* therefore, is seemingly dependent on these simple biologic and physiologic processes.

Dr Otto Saphir, of the Department of Pathology, checked our histologic interpretations.

EXPERIMENTAL PEPTIC ULCER PRODUCED BY CINCHOPHEN

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The administration of cinchophen is an effective method for producing chronic peptic ulcer in dogs. It may be said that the method is uniformly successful, depending on three conditions, they are (1) sufficient cinchophen administered over (2) a sufficient period to dogs which (3) take food every day. Surgical alteration of the gastrointestinal tract is not necessary for the production of this type of ulcer. The chronic ulcer is usually single and appears in the same region of the stomach in which it is noted in man, namely on the posterior wall near the lesser curvature and between the incisura and the pylorus. Infrequently an ulcer is seen on the anterior wall and none has been noted on the greater curvature. Duodenal ulcer occurs rarely and has been noted only in association with a larger gastric ulcer. The ulcer begins to heal with the discontinuation of administration of cinchophen and usually is completely healed within three or four weeks.

It is interesting to note that this type of experimental ulcer is preceded by acute gastritis, with multiple erosions. In most of our experiments gastritis has been a more prominent feature than it appears to be in association with the spontaneous ulcer occurring in man. This difference may be explained by the greater intensity of the processes employed experimentally, and it should be noted that experimental gastritis may be greatly reduced by lessening the amount of cinchophen administered. A chronic gastric ulcer may then occur in the presence of extremely mild gastritis which has been present for a longer time. The more complete evaluation of the factors concerned in the formation and healing of experimental ulcer should enable one to correlate more adequately than before the known facts concerning both experimental and clinical ulcer. It is obvious that the many additional factors which

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Read before the Section on Gastro-Enterology and Proctology at the Eighty-Eighth Annual Session of the American Medical Association Atlantic City, N. J. June 9, 1937

are present in the development and healing of ulcer in man preclude the direct application in their entirety of the results of experimental studies of ulcer to the condition as it occurs in man. However, errors made in the correlation of experimental and clinical observations arise from lack of detailed information concerning the factors involved rather than from any essential difference in the pathologic process.

Although cinchophen (atophan) was first prepared in 1887, gastric ulcer was not noted after its repeated administration until 1931, by Churchill and Van Wagoner.¹ They noted gastric ulcers in an examination of five of six dogs which had received cinchophen. In a more extensive study Van Wagoner and Churchill² (1932) produced acute and chronic peptic ulcers in dogs by the daily oral administration of cinchophen in amounts up to twenty-seven times the therapeutic dose for man. Single ulcers were seen, but multiple ulcers were frequently observed. The ulcers were in the gastric pathway near, or on, the lesser curvature. Duodenal ulceration occurred only in association with gastric ulceration. Churchill and Manshardt³ (1933) produced gastric ulcer in dogs by daily injection of cinchophen into an isolated loop of jejunum. They demonstrated that the ulcer was not caused by local toxic action of the drug directly on the gastric mucosa. Shoji⁴ (1933) gave cinchophen internally and parenterally to rabbits and dogs. He noted only gastritis in the rabbits, but both gastritis and ulcer occurred in the dogs. Barbour and Fisk⁵ (1933) and Bollman and Mann⁶ (1935) also noted gastric ulcer occurring in dogs after administration of cinchophen. Hanke⁷ (1934) produced gastritis and ulceration of the stomach in cats.

1 Churchill, T. P., and Van Wagoner, F. H. Cinchophen Poisoning, *Proc Soc Exper Biol & Med* **28** 581-582 (March) 1931.

2 Van Wagoner, F. H., and Churchill, T. P. Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning. Preliminary Report, *J A M A* **99** 1859-1860 (Nov. 26) 1932, Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning of Dogs, *Arch Path* **14** 860-869 (Dec.) 1932.

3 Churchill, T. P., and Manshardt, D. O. Experimental Production of Gastric and Duodenal Ulcers in Dogs in Cinchophen Poisoning, *Proc Soc Exper Biol & Med* **30** 825-827 (April) 1933.

4 Shoji, Arata. Ueber den Einfluss von Atophan auf die inneren Organe von Kaninchen und Hund, mit besonderer Berücksichtigung der Magenschleimhaut, *Tr Soc path jap* **23** 520-522, 1933.

5 Barbour, H. G., and Fisk, M. E. Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, Ethyl Ester of Paramethyl-Phenylcinchoninic Acid (Tolysin) and Sodium Salicylate, *J Pharmacol & Exper Therap* **48** 341-357 (July) 1933.

6 Bollman, J. L., and Mann, F. C. Experimental Production of Gastric Ulcers, *Proc Staff Meet, Mayo Clin* **10** 580-582 (Sept. 11) 1935.

7 Hanke, Hans. Ueber experimentelle akute Atophanylgastritis als Erscheinungsform einer vorwiegend toxisch bedingten Gastritis, *Beitr z path Anat u z allg Path* **94** 313-331 (Dec.) 1934.

after subcutaneous injection of cinchophen Schwartz and Simonds⁸ (1935) also observed ulcers in cats, but no ulcer was observed in rabbits or guinea pigs

Dodds and his co-workers⁹ (1934 and 1935) demonstrated some interesting results following parenteral and oral administration of an extract of the posterior lobe of the pituitary gland After a single large dose of the extract, severe gastritis, with an ulcerative process involving the entire acid-bearing portion of the stomach, was consistently produced in cats Repeated smaller doses produced a chronic gastric ulcer The authors suggested that this ulcer might be attributable to a gastrototoxic factor in the extract which is specific for the acid-secreting portion of the stomach

Reid and Ivy¹⁰ (1936) administered gastric mucin, 30 Gm twice daily, to dogs which also received cinchophen In all the dogs which received only cinchophen, gastroduodenal ulcer developed in from seven to fifty-nine days Ulcers were produced in but 18 per cent of the animals which received mucin and which were maintained sixty or eighty days, receiving the same amount of cinchophen as the control animals In addition, the animals which received mucin appeared to be more resistant to the acute toxic effects of the drug

METHODS OF INVESTIGATION

Normal dogs which received routine kennel care and a maintenance diet composed of ground meat, cracker meal and evaporated milk were used in these experiments A capsule containing cinchophen, usually from 100 to 200 mg for each kilogram of body weight, was given orally to each animal once daily, usually in the morning, at the same time that food was given In later experiments it appeared that chronic gastric ulcer was somewhat more uniformly produced if cinchophen was given for four consecutive days, followed by a period of rest of three days, with continuation of the diet Both the diet and the administration of cinchophen were varied, as was indicated in the various types of experiments All surgical procedures were performed while the animals were under surgical narcosis induced by ether, and an aseptic technic was carefully employed At the termination of the experiment the animals were killed with ether These and the dogs that died were examined completely, and gross and microscopic examination was made of the demonstrable lesions

8 Schwartz, S O, and Simonds, J P Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other Than the Dog, *Proc Soc Exper Biol & Med* **32** 1133-1134 (April) 1935

9 Dodds, E C, Noble, R L, and Smith, E R A Gastric Lesion Produced by an Extract of the Pituitary Gland, *Lancet* **2** 918-919 (Oct 27) 1934 Dodds, E C, Hills, G M, Noble, R L, and Williams, P C The Posterior Lobe of the Pituitary Gland Its Relationship to the Stomach and to the Blood Picture, *ibid* **1** 1099-1100 (May 11) 1935

10 Reid, P E, and Ivy, A C Gastric Mucin a Prophylactic Against Gastro-Duodenal Ulcers and "Acute" Toxicity Resulting from Cinchophen, *Proc Soc Exper Biol & Med* **34** 142-144 (March) 1936

Comment—The only lesions other than those of the stomach and duodenum that were noted were observed during the first ten days of administration of cinchophen¹¹. During this time a toxic condition usually developed, but it subsided after the first few days. The liver and kidneys of some animals killed during the initial stage of toxicity were slightly yellow. A variable degree of vacuolation of the hepatic cells and of the tubular epithelium of the kidneys was observed. Occasionally cloudy swelling was seen in the liver, and the degree of these changes appeared to be related to the degree of toxemia which had been produced by the dose of cinchophen. No gross or microscopic changes were noted in the other organs. At no time was jaundice observed, nor did the structural framework of the liver appear altered. The organs of the animals killed after the administration of cinchophen for from thirty to six hundred and thirty days appeared normal both grossly and microscopically except for the gastroduodenal lesions.

THE CINCHOPHEN ULCER

We found that feeding cinchophen will produce chronic peptic ulcer in nearly all dogs. The ulcer was usually single and was situated on the lesser curvature or on the posterior wall in the pyloric region (90 per cent). In about 35 per cent there were associated acute or subacute ulcers, which were frequently contact ulcers, situated just opposite and beyond the ulcer of the posterior wall. Associated duodenal ulcers of this type were observed in about 10 per cent of cases. Perforation of about 40 per cent of the chronic ulcers had occurred, but the result of perforation was death in only about half the group in which perforation occurred. In the group in which the result was not death perforation into the pancreas, liver, spleen or adjacent bowel had occurred. In about 30 per cent there was evidence of gross hemorrhage from the base of the ulcer, in a few cases this appeared to be the immediate cause of death.

During the course of administration of cinchophen certain signs and symptoms appeared to be characteristic. During the first few days the dogs appeared somewhat toxic, especially from one to six hours after administration of the drug. At these times they appeared stuporous but could be roused with little difficulty. If the animals refused food and administration of cinchophen was continued, the intoxication became more marked, but the incidence of formation of ulcer was definitely decreased. After a few days the animal again appeared normal for a short period. Usually during the second week emesis, as a rule of mild degree, occurred, and at about the same time watery diarrhea of variable

11 Stalker, L. K., Bollman, J. L. and Mann, F. C. Effect of Cinchophen on the Liver and Other Tissues of the Dog, *Proc. Soc. Exper. Biol. & Med.* **35** 158-160 (Oct.) 1936.

but increasing severity was noted. An ulcer was not noted before tarry stools had been observed, and it was almost always noted after this symptom had appeared. Some degree of anorexia and anemia usually was noted at this time, and often some loss of weight and decline in liveliness of the animal were noted. Death from perforation of the ulcer, or from hemorrhage, occurs more frequently during this stage of the procedure than during other stages, but in the absence of these complications the animals could be maintained for several months without much change in the appearance of the chronic ulcer. With the discontinuation of administration of cinchophen the animals rapidly returned to a normal-appearing condition.

Study of the stomachs removed from animals after varying periods of administration of cinchophen indicated the progression which occurs in the formation of this type of ulcer¹². Within the first few days the entire stomach appears somewhat edematous and hemorrhagic, and the mucosa is more or less covered with small linear hemorrhagic erosions, usually along the lesser curvature appear several superficial, clean-appearing, punched-out mucosal ulcerations which may be more than 1 cm in diameter. They rarely extend deeper than the muscularis mucosae. About one week later the hemorrhagic character of the gastric lesions is less marked, but there are numerous clean, superficial ulcerations of the fundic mucosa. In about another week the acute gastritis seems to have almost completely disappeared, and the number of acute ulcerations has greatly diminished. At this time a single, or at times a multiple, ulceration of the pyloric region appears marked. The lesions have a punched-out appearance and a necrotic base, although at this time the surrounding induration is not marked. Later the acutely ulcerated areas almost completely disappear, and the typical-appearing chronic ulcer remains on the posterior wall near the lesser curvature in the pylorus. Often the ulcer may be seen from the serosal surface as a group of fine, white radiating lines of fibrosis passing outward from the reddish center of the base of the ulcer.

Peptic ulcer caused by cinchophen heals in the same way as the experimental peptic ulcer described by Mann¹³ (1925) and the ulcer in man described by Caylor¹⁴ (1926). Within three days after discontinuation of administration of cinchophen the layer of necrotic tissue

12 Stalker, L. K., Bollman, J. L., and Mann, F. C. Experimental Peptic Ulcer Produced by Cinchophen. Methods of Production, the Effect of a Mechanical Irritant and the Life History of the Ulcer, *Arch Surg* **35** 290-308 (Aug) 1937.

13 Mann, F. C. Production and Healing of Peptic Ulcer. An Experimental Study, *Minnesota Med* **8** 638-640 (Oct) 1925.

14 Caylor, H. D. Healing of Gastric Ulcer in Man, *Ann Surg* **83** 350-356 (March) 1926.

over the base of the ulcer disappears. Within the next week the base of the ulcer is considerably elevated by the ingrowth of vascular granulation tissue, and a thin layer of pearly gray epithelium can be seen growing in from the sides of the ulcerated area. A few days later the granulation tissues are covered with a thin layer of epithelium, somewhat like normal gastric mucosa, which rapidly forms villi. The damaged muscular layers are at the same time replaced by fibrosis, and within four or five weeks complete healing has occurred. In place of the ulcer there is present a scar-filled excavation covered by a slightly atypical epithelium.

Peptic ulcer similar to that already described was produced by methods of administration of cinchophen in which the drug was not in direct contact with the gastric mucosa. Cinchophen administered in oil through a catheter inserted through a fistula into the jejunum or ileum produced gastric ulcer in dogs. Rectal administration produced similar results. Gastric ulcer was also produced after intravenous injections of a sodium salt of cinchophen and also by subcutaneous injections of cinchophen suspended in oil. In another group of dogs a Heidenhain pouch was made from an isolated portion of the fundus of the stomach. After the oral administration of cinchophen, acute and subacute perforating ulcers were present in the isolated pouch, which had not come in contact with the drug. In the stomach proper was a superficial ulceration which appeared to be less extensive than that usually seen in the unaltered stomach after similar exposure to cinchophen.

INFLUENCE OF CINCHOPHEN ON GASTRIC SECRETION

Studies made of gastric acidity by fractional analysis after a meal of meat before, during and after periods of administration of cinchophen failed to show any significant change in the level of gastric acidity produced by this stimulus.¹⁵ The secretion obtained just prior to feeding was frequently found to be of much greater volume and somewhat more acid during the periods of administration of cinchophen. Similar studies of the gastric secretion after subcutaneous injection of histamine failed to show significant changes in the acidity of the gastric juice. Secretion during fasting appeared to be definitely increased by cinchophen, and the total volume of gastric juice secreted after stimulation by histamine was found to be increased about twofold during the periods of administration of cinchophen. This increase appeared to be gradual, beginning after a few days of administration of cinchophen, and a definite peptic ulcer was always observed to be present when the volume of the secretion had reached its maximum. This hypersecretion

¹⁵ Stalker, L. K., Bollman, J. L., and Mann, F. C. Effect of Cinchophen on the Gastric Secretion. An Experimental Study, *Arch. Surg.* **34** 1172-1178 (June) 1937.

decreased rapidly when administration of the drug was discontinued, and it also was found to decrease markedly after an ulcer had been established, even though administration of the drug was continued. The activity of pepsin secreted by the stomach was not significantly altered by administration of cinchophen.

Studies of the fundic secretion from a Heidenhain pouch were quite comparable to those of the entire gastric secretion. Fractional analysis of the secretion from the pouch after a test meal disclosed no change in the concentration of the acid secreted, but the period of secretion was longer and more persistent during the first few days of administration of cinchophen. The total daily secretion was two or three times greater than the amount found before cinchophen was given. After the first few days ulceration of the pouch was present, and the contents were frequently contaminated with blood, but there appeared to be definite reduction in the volume of gastric juice secreted after ulceration was established. Ulcers appeared to form more rapidly in the acid-secreting pouch than in the stomach proper. We attributed this to the fact that some free acid was constantly present in the pouch and, in addition, there was little or no alkalinizing mechanism.

More than 90 per cent of the chronic ulcers that developed after the administration of cinchophen were in the pyloric region, which has an alkaline secretion, in contrast to the acid secretion of the rest of the stomach. After surgical exclusion of the pyloric segment of the stomach we were unable to produce ulceration in this area after administration of cinchophen. In other animals the excluded pyloric segment was made larger so that it included a portion of the acid-secreting fundic mucosa. Administration of cinchophen produced gastritis in the excluded pyloric segment of these animals, and acute or subacute ulcer was present in the pyloric region. Some gastritis was produced by the cinchophen in the stomach proper, and in about 40 per cent of the animals an ulcer developed on the posterior wall of the efferent loop of jejunum of the gastrojejunal anastomosis used to reestablish gastro-intestinal continuity after exclusion of the pylorus.

PROPHYLACTIC TREATMENT

The acidity of the gastric juice and the prolonged exposure of the pyloric mucosa to the action of acid appeared to be definite factors in the production of ulcers by cinchophen. We had also noted that in animals which refused food, ulcer sometimes developed more slowly than in others and that in animals fed a coarser diet, which included particles of bone, gastric ulcer developed more rapidly. These observations indicated that the consistency of the food likewise influences formation of ulcer. In the treatment of cinchophen peptic ulcer the attempt should be to give a nonirritating diet in such a manner that gastric acidity will

be at a minimum and that the ulcer-bearing area will be exposed to gastric contents for a minimal time¹⁶

Because the process of spontaneous healing when administration of cinchophen is discontinued is too rapid to allow certain evaluation of the effectiveness of therapy, we decided to determine the effect of prophylactic treatment on these ulcers. Accordingly, the forms of therapy were instituted simultaneously with the administration of cinchophen. Each of the dogs used was given a capsule containing 2 Gm of cinchophen each morning for the first four days of each week, on the last three days no cinchophen was given, but the usual diet and prophylactic treatment were continued. All animals were examined at the end of thirty days.

Animals of the control group received cinchophen in the same manner and were maintained on a diet of ground meat, cracker meal and evaporated milk. In every case a chronic peptic ulcer developed during the thirty days of study, a few of the animals died prior to this as a result of perforation of the ulcer.

Animals which received a diet composed wholly of milk, given in three feedings each day, also had gastric ulcers at the end of the period of administration of cinchophen. The process, however, was acute or subacute, in contrast to the chronic process in the control animals. The ulcers were also smaller and gave more evidence of healing than is usually seen.

Animals which received alkaline powders, bismuth subcarbonate, magnesium oxide, calcium carbonate and sodium bicarbonate six times during the day and a diet composed wholly of milk gave some evidence of gastritis during the first and second weeks but appeared normal during the later weeks. In no case did a chronic lesion develop. In the majority of the animals the stomach appeared normal at necropsy, but in others a few small mucosal erosions were present and some small healing lesions were observed.

Another group received gastric mucin, 15 Gm five times each day, in addition to the control diet. The appetite of these animals remained good, and their nutritional state appeared better than that of animals of the control groups. Two animals appeared entirely normal at necropsy, but two others which received the same treatment had a large chronic ulcer on the posterior wall near the pyloric ring.

Animals of another group were given duodenal extract, 3.3 Gm three times daily, in addition to the control diet. In every case there was some demonstrable lesion of the gastric mucosa, but in no case was the lesion as severe as that of the control group of animals. The usual

16 Stalker, L. K., Bollman, J. L., and Mann, F. C. Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, *Am J Digest Dis & Nutrition* 3: 822-827 (Jan) 1937.

picture after treatment with duodenal extract consisted, in part, of multiple small acute and subacute ulcerations

A daily intramuscular injection of 5 cc of a 4 per cent solution of histidine monohydrochloride was given to animals of another group which received cinchophen and the control diet. In each animal a larger chronic peptic ulcer developed and was as severe in every respect as any seen in the control group.

Animals of another group, which had been subjected to gastrojejunostomy, also were given cinchophen and the control diet. In each case symptoms of gastritis developed, but in no case had a gastric or gastrojejunal ulcer developed within the time allotted in these experiments. In most cases the jejunum appeared normal, but mild gastritis, with mucosal erosions, was present in the fundic portion of the stomach.

SUMMARY

The continued administration of cinchophen to dogs produces a chronic gastric ulcer similar in appearance and situation to the gastric ulcer of man. Formation of ulcer is preceded by the occurrence of acute gastritis which involves particularly the fundic portion of the stomach. After the first week or two the gastritis is less marked, and a perforating type of peptic ulcer develops on the pylorus. In a period as short as three weeks the ulcer may have all the appearance of a chronic peptic ulcer. Coarse foods decrease and soft foods increase the time required for formation of ulcer. During the period of the formation of ulcer the acidity of the gastric juice is within normal limits, but the amount of gastric juice secreted is definitely increased and the gastric content remains acid over a period longer than normal. Spontaneous healing of the chronic ulcer produced by cinchophen occurs rapidly when administration of the drug is discontinued. Complete healing may be accomplished in from two to seven weeks. Chronic ulcer did not occur after gastro-enterostomy under conditions which produced chronic ulcer in all the control animals. Chronic ulcer was not produced in dogs which received a diet of milk and alkaline powders. Other types of prophylactic therapy appeared to be less efficacious.

ABSTRACT OF DISCUSSION

DR GEORGE B. EUSTERMANN, Rochester, Minn. There is no denying the striking similarity between these experimental lesions and the chronic ulcer in the human being from the standpoint of physical appearance and behavior under treatment. If one could be sure that these two lesions were strictly comparable, then definitive conclusions bearing on etiology and treatment could be reached. Many of Dr. Bollman's observations are certainly verified by clinical experience, especially in regard to results of treatment by different methods, but certain paradoxes cannot easily be explained away by the clinician. For example, in the human being a toxic dose of cinchophen produces toxic hepatitis, often fatal, but rarely directly a chronic gastric lesion.

Again, the preponderant lesion, even in the experimental animal, is gastric and rarely, if ever, solely duodenal, and it is known that the converse is true in man, at least clinically. One may reasonably postulate that gastritis is the precursor of gastric ulcer, on the basis of combined clinical and histopathologic observations, but one still is faced with the fundamental problem. If so, what is the cause or genesis of gastritis in the human being with chronic ulcer usually encountered clinically?

These remarks are not to be construed as derogatory of the importance and brilliance of this and allied experimental studies, because these studies have yielded information concerning the mechanism of the production of ulcer that probably could not have been secured otherwise. In my opinion, however, the problem of the actual endogenous and exogenous factor or factors involved in the genesis of the chronic lesion still awaits solution.

DR LESTER R. DRAGSTEDT, Chicago. The experiments have been well planned, and the data secured are definite and instructive. They provide additional support to the large body of accumulated evidence which now points irresistibly to the digestive action of the gastric content as the important local factor in the genesis of ulcer.

The ulcers produced by Dr. Bollman and the associated gastritis are very similar to the lesions that I have observed develop in the totally isolated stomach of the dog, which I have interpreted as proving that pure gastric juice can digest all living tissues, including the wall of the stomach itself.

In the experiments of Dr. Bollman the secretion of gastric juice produced by cinchophen takes place in the empty stomach. There is no immediate neutralization by food. The gastric content is chiefly pure gastric juice, and the gastric mucosa is exposed to its digestive action in a manner similar to that obtaining in the isolated stomach.

The development of associated gastritis in both these experiments, that is those on the isolated stomach and those with cinchophen, is important, because it indicates that the ulcer gastritis described by Konjetzny is a part of the general process and, like the ulcer itself, is due to the corrosive action of the gastric content.

DR A. F. R. ANDERSEN, Brooklyn. The authors have called attention to the fact that the ulcers produced by cinchophen in the animals were exactly like the chronic gastric ulcers in human beings and that when the administration of cinchophen was stopped no new ulcers were noted and the chronic ulcers promptly healed. I want to point out that this is exactly what happens in the case of uncomplicated ulcer in man—a given ulcer heals rapidly and completely, as has been shown by clinicians and roentgenologists so many times and as has been emphasized particularly by Lewis Gregory Cole. An ulcer in man which fails to heal spontaneously is one which has been complicated by perforation against a neighboring viscus or by marked perigastric or periduodenal peritoneal reaction, resulting in a rigid area of infiltration which prevents the normal process of healing.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1937

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Two large books on allergy were published in 1937. The new edition of Albert H. Rowe's¹ book is entitled "Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria, and Other Causes: Manifestations, Diagnosis and Treatment." Louis Tuft's² book is entitled simply "Clinical Allergy." Both books cover the literature well and present the subject in all its aspects. In addition, several reviews of particular aspects of allergy are available in current journals. Francis Scott Smyth³ has presented a series of critical reviews of allergic disease, the last two being published in the *Journal of Allergy* and in the *Journal of Pediatrics*. Hansel⁴ once more reviews the current literature on allergy as related to otolaryngology and ophthalmology. Feinberg⁵ presents "Progress in Asthma and Hay Fever, the Literature for 1936," and Sulzberger⁶ writes on the "Allergic Manifestations of Dermatology." In my review of the literature of 1936⁷ I tried to lay stress on the significance of the allergic reaction and on the relation between allergy and immunity.

1 Rowe, Albert H. Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes: Manifestations, Diagnosis and Treatment, Philadelphia, Lea & Febiger, 1937.

2 Tuft, Louis. Clinical Allergy, Philadelphia, W. B. Saunders Company, 1937.

3 Smyth, Francis Scott. Allergic Diseases in Childhood. Critical Review, *J Allergy* 8: 89, 1936, *J Pediat* 8: 500, 1936.

4 Hansel, French K. Allergy as Related to Otolaryngology and Ophthalmology. Literature for 1936, *J Allergy* 8: 196, 1937.

5 Feinberg, Samuel M. Progress in Asthma and Hay Fever. Literature for 1936, *J Allergy* 8: 280, 1937.

6 Sulzberger, M. B. Allergic Manifestations in Dermatology, *New York State J Med* 36: 1717, 1936.

7 Rackemann, Francis M. Allergy. A Review of the Literature of 1936, *Arch Int Med* 59: 144 (Jan) 1937.

The importance of the allergic reaction is shown well by the work of Willis and Woodruff,⁸ who studied the state of immunity in desensitized animals and compared the development of tuberculous lesions in normal, allergic and desensitized animals. They gave large doses of living tubercle bacilli to three groups of guinea-pigs. The first group was made up of normal animals. When inoculated with virulent tubercle bacilli they became allergic, and scattered tubercles developed in the lungs, many died of extensive disease. The second group of animals had recovered from a previous injection of avirulent tubercle bacilli. They had become allergic. After reinoculation with virulent bacilli the animals remained allergic, and only a few died, with moderate tubercle formation in the lungs. The third group was made up of normal animals in which the development of allergy was prevented by a daily dose of 1 cc of old tuberculin given (presumably) subcutaneously. In the absence of allergy the animals died promptly of generalized tuberculous bronchopneumonia when given the final test dose. As Dienes⁹ points out so well, true immunity is a function of the tissues, and the allergic reaction is merely a part of this tissue immunity. Free antibodies in the serum represent merely the excess.

Meantime, greater stress is being laid on the importance of using materials which are strictly pure. For example, Abernethy and Francis¹⁰ studied the cutaneous reactions of patients with pneumonia to the cellular carbohydrate fraction C of the pneumococcus. They found that the positive cutaneous reaction develops early in the disease and tends to fade with recovery. It runs parallel to the development of precipitins for the same C fraction. In fatal cases a positive cutaneous reaction to fraction C never does develop. The reaction to fraction C is different in its time of appearance from the reaction to the other carbohydrate—the capsular substance, or the so-called soluble specific substance (SSS). The latter elicits no reaction until recovery is definitely established. In a second paper Abernethy¹¹ compares the response in rabbits infected with virulent pneumococci given intradermally with the reaction in monkeys treated with the same organism injected directly into the bronchi. These virulent bacteria caused the

8 Willis, H. S., and Woodruff, C. E. Allergy and Desensitization in Tuberculosis, *J. Clin. Investigation* **16** 899, 1937.

9 Dienes, Louis, and Naterman, H. L. Immunological Response to Vaccinia in Guinea Pigs, *J. Infect. Dis.* **60** 279, 1937.

10 Abernethy, Theodore J., and Francis, Thomas, Jr. Studies on the Somatic C Polysaccharide of Pneumococcus. I. Cutaneous and Serological Reactions in Pneumonia, *J. Exper. Med.* **65** 59, 1937.

11 Abernethy, Theodore J. Studies on the Somatic C Polysaccharide of Pneumococcus. II. The Precipitation Reaction in Animals with Experimentally Induced Pneumococcal Infection, *J. Exper. Med.* **65** 75, 1937.

development of tremendous hemorrhagic local lesions in rabbits with death in three or four days. These animals never showed positive cutaneous reactions. In the monkey, on the other hand, a precipitin reaction developed promptly and remained until recovery began. Cutaneous tests were not made.

Stevens and Jordani¹² extend and clarify their own work by showing that when a group of patients with asthma, hay fever and other miscellaneous diseases were tested intradermally with nucleoproteins from *Staphylococcus aureus* and a hemolytic streptococcus urticarial reactions were obtained only in that group of patients who had evidence of true hypersensitiveness to common allergens. On the other hand, delayed inflammatory reactions were evenly distributed among patients of all kinds. In the discussion the authors say that they are doubtful whether the immediate reaction depended strictly on the nucleoprotein or some trace of the bacterial carbohydrate which might have been mixed with it.

In December 1936 Opie¹³ published an excellent discussion of the significance of allergy in disease. This article is most timely and should be read by every one interested in the subject. In it Opie points out again that the local reaction which is so characteristic of allergy has the function of holding the infecting agent fixed at the site of inoculation. If this reaction is produced by injection of formed substances (foreign red cells or tubercle bacilli) these elements are not destroyed by the reaction, they stay intact for some time. The function of the allergy is merely to hold them in place. Allergy is closely related to immunity, but the two are not necessarily parallel. Opie reviews the details of recent works on the reaction of animals to tubercle bacilli, to nonhemolytic streptococci and to hemolytic streptococci and shows that, with minor variations dependent chiefly on the virulence (invasiveness) of the organism, the reactions are much the same in each case. If the infecting agent is not too virulent, so that it does not spread too rapidly because of its own invasive power, it remains at the point of entrance, and up to that time allergy and immunity develop together. Later, sensitization occurs, so that if the antigen is injected a second time an immediate response is elicited, and the second dose is held with considerable effectiveness to the site of injection. However, this allergy can be abolished temporarily by the injection of the antigen intravenously. In this process of rapid desensitization the immunity is not affected. Circulating antibodies, as measured by complement fixation,

12 Stevens, F. A., and Jordani, L. Delayed and Immediate Reactions to Bacterial Nucleo-Proteins in Asthma, Hay Fever and in Group of Miscellaneous Diseases, *J. Immunol.* **31** 477, 1936.

13 Opie, E. L. The Significance of Allergy in Disease, *Medicine* **15** 489, 1936.

remain in the same concentration as before. Desensitized animals are still resistant to ordinary doses of the infecting agent given intravenously.

These relations show considerable variation among animals and with the different varieties of infectious agents. As has been implied, the allergic reaction is more easily demonstrated with infections of low virulence. The technic is also important, and, especially in the case of streptococci, allergy can be demonstrated only when the organisms are injected into the skin itself, it never occurs in animals treated intravenously. The technic also includes the products used, and Opie makes the interesting suggestion that virulence and the capacity to induce sensitiveness may depend on different parts of the antigen—a thought which emphasizes again the point that whole bacteria and many of their so-called purified products are really mixtures of different antigenic principles. The paper by Abernethy and Francis¹⁰ is especially interesting in this regard.

These studies of the various features of bacterial allergy advance the knowledge of the mechanism of "clinical allergy"—that special form dominated by cutaneous and tissue reactions of the immediate urticarial type. The development of immediate reactions to certain carbohydrate fractions of the pneumococcus is part of the normal immune process in pneumonia, just as the immediate reaction is part of the normal response when a large dose of foreign serum is given to a normal person. The immediate reactions, which are called hay fever, asthma or eczema, may well be a simple exaggeration of a process which is fundamentally normal.

The delayed inflammatory reactions produced by other bacterial products are closely related, as previously discussed. Vaccines influence the progress of asthma. Their effect is nonspecific and is related to the local reactions which they produce. However, the mechanism of their action is not yet understood clearly.

THE NATURE OF CLINICAL ALLERGY ("ATOPY")

Heredity—The nature and origin of clinical allergy remain obscure, despite an enormous amount of work. It is generally agreed that heredity plays an important, if not an essential, part in the origin of allergy, and it is refreshing to have Ratner¹⁴ say that in an intensive study of 250 allergic children, 350 normal children and their respective families the incidence of allergy in the family of the allergic child was found to be approximately the same as that in the family of the normal

14 Ratner, Bret. Does Heredity Play a Role in the Pathogenesis of Allergy? *J. Allergy* 8 273, 1937.

child Baagøe¹⁵ describes the occurrence of allergy in Denmark pointing out that a familial predisposition can change the incidence of asthma, for example, from 3 to 7 per cent Spaich and Ostertag¹⁶ made an allergic study of seventy-one pairs of twins In the case of uniovular twins the same type of allergic manifestation appeared in each member of the pair in a high percentage of cases This was especially true of hay fever, migraine and urticaria For asthma, however, the figures were lower, since asthma occurred in only 28 per cent In the case of biovular twins the figures were lower The authors believe that these results constitute a clear demonstration of the importance of heredity

Endocrine Factors—Endocrine factors are always to be considered, but so far there is little supporting evidence in this regard Dragstedt Mills and Mead¹⁷ tried to protect dogs against fatal anaphylactic shock with a previous injection of an extract of adrenal cortex, and although in the animals so treated the severity of the resulting reactions was less marked, it is proper to point out that nonspecific therapy of various sorts can likewise modify the severity of shock In 1936 Wilmer Miller and Beardwood¹⁸ reported that the curve for dextrose tolerance is altered in the allergic state and pointed to the rarity of the occurrence of allergy and of diabetes in the same patient More recently they¹⁹ have shown that for 633 patients with allergy the average sugar curve rose only to 130 mg, whereas for the controls it reached 160 mg Wagner and Rackemann²⁰ also determined the sugar tolerance of patients with asthma but failed to find any significant difference from that of normal persons Even for the chronic users of epinephrine, the sugar curve was still in its normal position

Dietary Factors—The dietary factors are a little more pertinent and this year several articles deal with the influence of vitamins on anaphylaxis and allergy Van Niekerk,²¹ in Holland, produced scurvy in guinea-pigs and found that the animals reacted to horse serum as do normal animals, and, furthermore, that a large dose of vitamin C had

15 Baagøe, K H Occurrence of Allergic Diseases Among Danish Population and Role of Predisposition, *Hospitaltid* **79** 888, 1936

16 Spaich, D, and Ostertag, M Study of Allergic Disease in Twins, *Ztschr f menschl Vererb- u Konstitutionslehre* **19** 731, 1936

17 Dragstedt, C A, Mills, M A, and Mead, F B Adrenal Cortex Extract in Canine Anaphylactic Shock, *J Pharmacol & Exper Therap* **59** 359, 1937

18 Wilmer, H B, Miller, M M, and Beardwood, J T Recent Advances in the Diagnosis and Treatment of Allergic Disease, with Special Reference to Glucose Tolerance and Metabolism, *South M J* **29** 197, 1936

19 Wilmer, H B, and Miller, M M Glucose Tolerance and Metabolism in Allergic Individual, with Report of Glucose Tolerance Observations in Six Hundred Patients, *Pennsylvania M J* **40** 505, 1937

20 Wagner, Harold C, and Rackemann Francis M Triplicate Determinations of Sugar Tolerance in Mild and Severe Asthma, *J Allergy* **8**:353, 1937

21 van Niekerk, J Anaphylaxis and Vitamin C *J Allergy* **8** 446 1937

no protective effect against anaphylactic shock. On the other hand, in a study of patients with asthma Epstein²² found that vitamin C was a useful adjuvant to other treatment. In this connection it is interesting to note the experiments of Jungeblut,²³ who found that the addition of optimal quantities of vitamin C to the diet of monkeys would protect a certain number against an otherwise fatal dose of poliomyelitis virus. It is possible, of course, that vitamins may influence all the processes of immunity. The old difficulties concerning the production of cutaneous sensitiveness to arsphenamine—that certain animals would respond while others would not—are modified somewhat by the findings of Cormia,²⁴ who discovered that a diet low in vitamin C made it possible to produce sensitiveness to arsphenamine in guinea-pigs which on a full diet did not react. When huge doses of vitamin C were given to other guinea-pigs, they could not be sensitized at all.

Chemical Mediators of Nervous Activity—Finally, the new knowledge of chemical mediators of nervous activity makes it proper to entertain the theory that the manifestations of allergy may depend on some peculiar response of the body to a substance like acetylcholine, sympathin or histamine, which are normal products of the tissue and which are known to exert powerful effects.

This important subject is reviewed in a new book by Cannon,²⁵ who describes the organization of the autonomic system and the evidence of the chemical mediation of nervous impulses. The extraordinary substances discovered through the experiments of Hunt, Dale, Loewi and Cannon are described as to their immediate and their remote effects and in relation to each other.

When the sympathetic nervous system is stimulated, epinephrine is poured out into the blood stream by the adrenal glands, and, in addition, another substance (discovered by Cannon and his co-workers), called sympathin, is secreted by the cells in which the sympathetic nerves have their ending, such as the cells of the smooth muscle of blood vessels or of the intestines. Epinephrine and sympathin are called sympathomimetic (they "mimic" the symptoms of sympathetic stimulation) or, better, adrenergic substances (in contrast to cholinergic substances).

The chemical mediator of the parasympathetic system is different. The parasympathetic, sometimes called the vagus, system, includes the

22 Epstein, A. Use of Vitamin C in Treatment of Bronchial Asthma, *Schweiz med Wchnschr* **66** 1087, 1936.

23 Jungeblut, Claus W. Vitamin C Therapy and Prophylaxis in Experimental Poliomyelitis, *J Exper Med* **65** 127, 1937.

24 Cormia, F. E. Experimental Arsphenamine Dermatitis. Influence of Vitamin C in Production of Arsphenamine Sensitiveness, *Canad M A J* **36** 392, 1937.

25 Cannon, Walter B., and Rosenbleuth, Arturo. *Autonomic Neuro-Effector Systems*, New York, The Macmillan Company, 1937.

third, seventh, ninth and tenth cranial nerves, as well as the spinal (sacral) nerves which supply the rectum, bladder and genitals. When a parasympathetic nerve is stimulated, the corresponding cells produce a substance which on application to new cells is capable of reproducing the same symptoms as the original stimulation. As Loewi showed, the perfusate from a heart slowed by action of the vagus system could cause slowing in a second heart when infused into it. The substance responsible has the physical and chemical characteristics of acetylcholine. It has many interesting properties. First of all, it is extremely labile, being readily destroyed in the body by blood and by tissue extracts, for the reason that these tissues contain a ferment for it called choline esterase. This ferment, however, can in turn be readily neutralized by physostigmin or prostigmin, so that if the whole animal or the blood tissue extract is treated with physostigmin, acetylcholine will then degenerate only very slowly, and thus its effect will be much more evident. Blood alone can destroy acetylcholine, but the blood of certain animals does it faster than that of others. It is noteworthy that when the various vertebrates are arranged according to the breakdown of acetylcholine in the blood, the order being from strongest to weakest (man, pig, cow, dog, horse, rabbit, frog, cat and guinea-pig), this order is not very different from the order of their susceptibility to anaphylactic shock.

Histamine also is a product of the normal cell and has functions much like those of acetylcholine, but histamine is stable.

Pilocarpine hydrochloride has an action comparable to that of acetylcholine. Dharmendra²⁶ tested the drug on 47 asthmatic patients and 11 controls and found marked responses in 30 of the asthmatic patients but in only 2 of the controls.

Anesthetics like ether prevent the development of those symptoms which provide the demonstration of the presence of acetylcholine. Ethyl carbamate (urethane) seems to interfere with the liberation of acetylcholine in the tissues, and it is interesting that Farmer²⁷ has shown that it can protect guinea-pigs against fatal anaphylactic shock. When the uterine horn of the sensitized guinea-pig was treated with ethyl carbamate and then with the specific serum, no contraction occurred, and yet the uterus was found desensitized to further doses of the antigen. In case the ethyl carbamate was washed out of the bath before the sensitive serum was added, then contraction occurred. The authors conclude that ethyl carbamate acts simply to inhibit the contraction, it does not prevent the specific union of antigen and antibody.

²⁶ Dharmendra. Response to Pilocarpine in Cases of Asthma, *Indian M. Gaz.* **71** 204, 1936.

²⁷ Farmer, Lawrence. The Influence of Urethane on Anaphylactic Reactions. A Contribution to Dale's Theory of Anaphylaxis, *J. Immunol.* **33** 9, 1937.

Benzedine (racemic benzylmethylcarbinamine) is a drug new to the treatment of asthma. It has pronounced adrenergic effects and is useful in cases of mild asthma as a temporary measure. When administered over a long period it may do harm.

At the 1937 meeting of the American Medical Association, in Atlantic City, N. J., Myerson²⁸ had an exhibit showing the relations in the field of human autonomic pharmacology. Mecholyl (acetyl beta-methylcholine hydrochloride) is a relatively stable substance which can be used to reproduce the effects of acetylcholine. When injected into a normal person it produces a marked reaction, with flushing of the face, sweating, narrowing of the pupils, rhinorrhea and perhaps asthma.²⁹ The heart is slowed and intestinal peristalsis is accelerated. Gastric secretion is much increased. All these symptoms can be quickly abolished with atropine, so that Dameshek and Fensilver³⁰ suggest that mecholyl may be used in a diagnostic test for atropism.

The idea that asthma (and, indeed, other symptoms of allergy) may depend on an excess of acetylcholine, on some disturbance in its normal breakdown by the esterase or on some peculiar sensitivity to it is of considerable interest. In 1934 Villaret, Valléry-Radot, Bezançon and Claude³¹ found that from 0.02 to 0.04 Gm. of pure acetylcholine given to a patient with asthma caused an attack at once but that in normal persons asthma did not occur, except in patients who had recently recovered from pneumonia. This exception led them to the finding that asthma could be produced also in dogs with acetylcholine, provided the lungs were irritated by exposure to chlorine gas. Evidently this preliminary irritation of the lungs is necessary. Foggie³² also has shown that both histamine and acetylcholine can cause bronchoconstriction in the lungs of the rat, as expected, the rat requires larger doses than the guinea-pig.

28 Myerson, A. Human Autonomic Pharmacology, *J. A. M. A.* **110** 101 (Jan. 8) 1938.

29 Starr, I., Jr., Elsom, K. A., Reisinger, J. A., and Richards, A. N. Acetyl- β -Methyl Choline. Action on Normal Persons with Note on Action of Ethyl Ether of β -Methylcholine, *Am. J. M. Sc.* **186** 313, 1933. Starr, I., Jr. On the Treatment of Paroxysmal Tachycardia and Certain Other Disturbances of Cardiac Rhythm by Acetyl- β -Methylcholine, *Tr. A. Am. Physicians* **50** 289, 1935.

30 Dameshek, W., and Fensilver, O. Human Autonomic Pharmacology. The Use of Acetyl-Beta-Methyl Choline Chloride (Mecholyl) as a Diagnostic Test for Poisoning by the Atropine Series of Drugs, *J. A. M. A.* **109** 561 (Aug. 21) 1937.

31 Villaret, M., Valléry-Radot, P., Justin-Besançon, L., and Claude, F. Recherches préliminaires sur les crises provoquées chez les asthmatiques par certains esters de la choline, *Compt. rend. Soc. de biol.* **116** 1343, 1934. Crises asthmatiformes expérimentales provoquées par l'administration de vagomimétiques, après irritation pulmonaire, *ibid.* **124** 1308, 1937.

32 Foggie, P. The Action of Adrenaline, Acetyl Choline and Histamine on the Lungs of the Rat, *Quart. J. Exper. Physiol.* **26** 225, 1937.

Several experiments aim to show that the effects of cholinergic substances are increased during shock and therefore that perhaps the shock depends on them. Ungar and Parrot³³ made extracts of guinea-pig lung before and after sensitization to horse serum and tested them on strips of guinea-pig intestine. The extract of sensitized lung mixed with horse serum gave a definite contraction curve, whereas the controls showed no reaction. Dragstedt and Mead,³⁴ with a similar experiment, found that a histamine-like substance was present in the blood during anaphylactic shock in the dog. Corelli³⁵ observed that an injection of histamine intensified eczematous lesions of the skin by producing an increased permeability of the capillaries. In cases of asthma Wenner and Buhrmester³⁶ determined the acetylcholine content of the blood and found it increased. If anaphylactic shock and asthma are associated with an excess of cholinergic substances, perhaps a part of the picture depends on a depletion of adrenergic substances. Koref and Rivera³⁷ found that after shock, whether produced by histamine, peptone or anaphylaxis, the epinephrine content of the adrenal glands is decreased.

Reagents—Once a state of allergy develops, it is said that symptoms result from the union of the antibody and the antigen in the sensitized cell. The Prausnitz-Kustner phenomenon furnishes one method of demonstrating the presence of this antibody, but several new observations have been made on it. Stull, Sherman and Cooke³⁸ found that the active principle is contained in the pseudoglobulin of the sensitizing serum. Parlato³⁹ found that blister fluid also could transfer sensitiveness from patient to normal recipient. Sherman, Kaplan and Walzer⁴⁰ demon-

33 Ungar, G, and Parrot, J. L. Recherches sur le choc anaphylactique in vitro. Mise en liberte d'une substance active par le poumon isole du cobaye sensibilise. *Compt rend Soc de biol* **123** 676, 1936.

34 Dragstedt, C. A., and Mead, F. B. Role of Histamine in Canine Anaphylactic Shock, *J Pharmacol & Exper Therap* **57** 419, 1936.

35 Corelli, F. Intensification of Cutaneous and Visceral Allergy from Histamine Injection, *Policlinico (sez. med.)* **44** 491, 1937.

36 Wenner, W. F., and Buhrmester, C. C. Potassium and Acetylcholine of the Blood of Rabbits in Anaphylactic Shock, *J Allergy* **9** 85, 1937.

37 Koref, O., and Rivera, M. Ueber den Adrenalinhalt der Nebennieren im Anschluss an den Histamin-Pepton- und anaphylaktischen Schock, *Wien med Wchnschr* **87** 184, 1937.

38 Stull, A., Sherman, W. B., and Cooke, R. A. The Association with Pseudoglobulin of the Skin Sensitizing Substance of Allergic (Hay Fever) Serum, *J Allergy* **9** 7, 1937.

39 Parlato, S. J. Use of Blister Fluid for Passive Transfer Skin Test, *J Allergy* **7** 573, 1936.

40 Sherman, H., Kaplan, C., and Walzer, M. Studies in Mucous Membrane Hypersensitiveness. II. Passive Local Sensitization of the Nasal Mucous Membrane, *J Allergy* **9** 1, 1937.

strated that when the reagenic serum was injected into the nasal mucosa over the turbinates or septum, injection of antigen into these same sites resulted in local swelling, but rarely in symptoms simulating hay fever Caulfeild, Brown and Waters ⁴¹ and, almost at the same time, Straus ⁴² succeeded in transferring local sensitiveness to allergens like horse serum or cotton-seed from man to monkey These findings are of considerable interest because up to that time the attempts to reproduce the transferred phenomena had not been successful in the lower animals Caulfeild ⁴¹ also succeeded in transferring a local sensitiveness from guinea-pigs to monkeys

What is the significance of the so-called reagins? It has been thought that they are responsible for the symptoms of allergy, and much stress has been laid on the positive demonstration of reagins as evidence of hypersensitiveness to a particular foreign substance Now comes a paper by Chobot and Hurwitz ⁴³ in which it is shown that reagins may frequently be demonstrated in the serum of children "skin sensitive" to food in spite of the fact that they have no corresponding clinical manifestations Hill ⁴⁴ found reagins to dust and feather proteins in 6 of 16 children tested One point stressed in his paper is that neither cutaneous tests nor reagins are proof of clinical sensitiveness

Reagins have long been used as a means of study of biologic relations between related substances Baldwin and Benedict ⁴⁵ in this way studied the crossed reactions to various botanically related foods and found that when the serum of a sensitive patient was incubated with extracts of the food, all the reagins to members of the food group were neutralized at the same time Thus, carrot, celery, parsley and parsnip are biologically related, likewise, apple, quince and pear Three fishes were found to be related Studying different household dusts, including house dust, kapok and feathers, Wagner and I ⁴⁶ found a certain cross-relation

41 Caulfeild, A H W , Brown, M H , and Waters, E T Suitability of the Monkey (*Macacus Rhesus*) as a Recipient for the Prausnitz-Kustner Reaction, *Proc Soc Exper Biol & Med* **35** 109, 1936, Concerning the Identity of the Antibody in Experimental Anaphylaxis and That Occurring in Man Naturally or Spontaneously Sensitized, *J Lab & Clin Med* **22** 657, 1937

42 Straus, H W Studies in Experimental Hypersensitiveness in the Rhesus Monkey II Passive Local Cutaneous Sensitization with Human Reagenic Sera, *J Immunol* **32** 251, 1937

43 Chobot, Robert, and Hurwitz, George The Limitation of Passive Transfer in Food-Sensitive Children, *J Allergy* **8** 427, 1937

44 Hill, Lewis Webb Sensitivity to House Dust and Goose Feathers in Infantile Eczema The Role of Specific Allergens, *J Allergy* **9** 37, 1937

45 Baldwin, H S , and Benedict, M I Mutual Absorption Tests with Related Foods, *J Allergy* **8** 120, 1937

46 Wagner, Harold C , and Rackemann, Francis M Crossed Reactions to Household Dusts, *J Allergy* **8** 537, 1937

between the different substances, but the relation was not absolute. Regarding specificity, Hooker⁴⁷ recalls the theoretical reasons for the conception that whole molecules are not involved in specific reactions but that specificity is determined only by the small binding groups on these molecules. For example, animals prepared with iodized horse serum react to iodized chicken serum as well as to normal horse serum.

Can clinical sensitivity be present in patients who have no reagins? The question is important, but it is hard to answer. "Test-negative" patients appear to be clinically sensitive, and special tests prove that they are, but so far no one has looked for reagins in their blood.

CHEMISTRY OF HYPERSENSITIVENESS

The chemistry of hypersensitiveness has been advanced a little. Landsteiner⁴⁸ studied trinitrophenol hydrochloride and 2,4-dinitrochlorobenzene and their ability to combine with blood serum and to produce anaphylactic shock. His animals that had been treated, however, reacted not to the chemical itself but only to its protein combination, the reaction obtained included positive cutaneous reactions as well as anaphylaxis of the entire body. Fierz, Jadassohn and Stoll⁴⁹ made similar studies of atoxyl (sodium arsanilate) combined with protein by diazotization. As expected, the protein combination seemed to be essential.

CLINICAL ALLERGY

Diagnosis—The diagnosis of allergy, particularly the interpretation of positive cutaneous reactions, is discussed in an interesting paper by Pearson⁵⁰. He made cutaneous tests on a large number of asthmatic and control subjects and observed that positive reactions occurred in many of the controls, although, of course, more were found among the asthmatic subjects. He describes the cutaneous test as a source of "subsidiary information." Another good paper is by Pratt,⁵¹ who recalls the theory that atopic symptoms can depend on the summation of a slight degree of sensitiveness to a number of different allergens acting together. Pratt put this theory to a test by studying the anaphylactic reaction in

47 Hooker, S. B. Different Determinants of Antigenic Specificity on Single Molecules, *J. Allergy* 8:113, 1937.

48 Landsteiner, K., and Chase, M. W. Studies on the Sensitization of Animals with Simple Chemical Compounds. IV. Anaphylaxis Induced by Picryl Chloride and 2,4-Dinitrochlorobenzene, *J. Exper. Med.* 66:337, 1937.

49 Fierz, H. E., Jadassohn, W., and Stoll, W. Anaphylactic Sensitization with Chemically Definite Compounds, *J. Exper. Med.* 65:339, 1937.

50 Pearson, R. S. B. Observations on Skin Sensitivity in Asthmatic and Control Subjects, *Quart. J. Med.* 6:165, 1937.

51 Pratt, Henry N. Anaphylaxis in Multiply Sensitive Guinea Pigs, *J. Allergy* 9:14, 1937.

guinea-pigs sensitized to crystallized egg albumin and to crystallized horse globulin at the same time. He concludes, first, that when the test dose contains a small amount of each antigen the degree of shock is not more than would be observed from the same small amount of either antigen alone, and, second, that when either of the antigens is increased by itself above the minimum requirement, the incidence of shock and its severity are increased definitely. Why the body should not react to each of two substances at the same time is, of course, still difficult to explain, unless it is that the molecule of one substance is larger than that of the other, so that the animal reacts first to the one which can permeate his tissues with greater ease.

The diagnosis of specific factors depends entirely on the interpretation of cutaneous tests, and Hill ⁴⁴ has thrown an interesting light on this subject. He tested 44 eczematous infants with a stock extract of house dust and an extract of feathers intradermally and found that 31 of the infants reacted to the dust and 25 to the feathers. Normal children did not react. Other allergic children did not react. What did these positive reactions mean? Sometimes elimination of external dust by confinement in a hospital room was enough to bring relief, but there were too many exceptions to this principle, so Hill points out again that there must be an obvious distinction between sensitiveness of the skin, on the one hand, and clinical sensitiveness of the whole body, on the other. The one situation in which a real cure occurs is that which follows acute infectious diseases. And here lies the important key to the problem. The article closes with a good line: "The removal of allergens is a surrender to a bad situation rather than a direct attack upon it." The next two papers are practical. Swineford ⁵² describes a woman of 32 who always obtained great relief from wheezing by smoking asthma powder containing Stramonium, swamp cabbage, Lobelia inflata and potassium nitrate until finally she became sensitive to the dust of the powder itself. Bernstein and Ginsberg ⁵³ had a patient who became sensitive to the milk preparation used in nonspecific therapy.

The leukopenic index of Vaughan ⁵⁴ still has its advocates. Squier and Madison ⁵⁵ note that the number of eosinophil cells in the blood increases as constantly as the number of leukocytes falls after the inges-

52 Swineford, Oscar J. Hypersensitiveness to "Asthma Powders," *J Allergy* 8 607, 1937.

53 Bernstein, C, Jr., and Ginsberg, J. E. Sensitization to Milk as a Result of Its Use in Non-Specific Foreign Protein Therapy, *J A M A* 108 193 (Jan 16) 1937.

54 Vaughan, Warren T. Food Allergens. III The Leucopenic Index, *J Allergy* 5 601, 1934.

55 Squier, T. L., and Madison, F. W. The Hematologic Response in Food Allergy. Eosinophilia in the Leucopenic Index, *J Allergy* 8 250, 1937.

tion of allergic foods. On the other hand, Loveless and her associates⁵⁶ studied the leukocyte reaction of a number of patients who were known to have allergic symptoms after the ingestion of certain foods. In some of these she observed that the taking of food caused a rise rather than a fall in the total leukocyte count. Also, leukopenia was found in some normal persons after a test breakfast. Her work in this report was most meticulous, each observation being based on a count of 800 white cells.

Waldbott and Ascher⁵⁷ showed that when cutaneous tests are made less than four weeks after the original onset of asthma, they are likely to give a negative reaction.

The diagnosis and the therapy of serum reactions, with general rules to be followed before any foreign serum is administered to a patient, are well given in a special article in *The Journal of the American Medical Association* by Fantus in collaboration with Feinberg.⁵⁸

A good point is raised by Gilles,⁵⁹ who says that the fear of anaphylaxis can no longer justify the failure to employ protective serum in every case of street accident. He examined sixty-three samples of dust from the streets of Baltimore and found tetanus bacilli in 17.4 per cent of them. Furthermore, nine of the eleven strains, or 14.2 per cent of the samples, contained a virulent toxin-producing organism. Not only is treatment with tetanus antitoxin advisable, but it should always be given early, for, as Huntington and his colleagues⁶⁰ point out in a study of 642 cases, the mortality from tetanus is very high, regardless of whether or not the patient is treated with serum.

Other diagnostic procedures include the study of the blood lipids, but Bullen and Bloor⁶¹ found no difference between the patient with asthma and the normal control in this regard. Black and Kemp⁶² found that the density of the blood, as measured by timing the rate of fall of a small drop of blood through a mixture of xylene and bromobenzene, was increased in cases of guinea-pig anaphylaxis and certain forms of allergy.

56 Loveless, Mary, Downing, L., and Dorfman, R. Leucopenic Index, *J Allergy* 8 276, 1937.

57 Waldbott, G. L., and Ascher, M. S. Skin Reactivity in Cases of Asthma of Short Duration, *J Allergy* 8 246, 1937.

58 Fantus, Bernard, and Feinberg, S. M. The Therapy of (Horse) Serum Reactions. General Rules in the Administration of Therapeutic Serum, *J A M A* 107 1717 (Nov. 21) 1936.

59 Gilles, Eric C. The Isolation of Tetanus Bacilli from Street Dust. Its Bearing on Surgical Practice, *J A M A* 109 484 (Aug. 14) 1937.

60 Huntington, R. W., Jr., Thompson, W. R., and Gordon, H. H. Treatment of Tetanus with Antitoxin. Analysis of Outcome in Six Hundred and Forty-Two Cases, *Ann Surg* 105 93, 1937.

61 Bullen, S. S., and Bloor, W. R. Lipids of the Blood Plasma in Hay Fever and Asthma, *J Allergy* 8 155, 1937.

62 Black, J. H., and Kemp, H. A. Blood Density in Guinea Pig Anaphylaxis and in Hay Fever Artificially Induced. *Am J Clin Path* 7 300 1937.

HAY FEVER

Pollen—Wodehouse⁶³ adds several articles to his series of botanic descriptions of the different "hay fever plants" Stealy⁶⁴ describes the pollen content of the air over San Diego, Calif, and Schonwald⁶⁵ gives a general description and some good pictures of the pollens which are common to Seattle Blumstein and Tuft⁶⁶ call attention to the importance of plantain as a fairly frequent cause of hay fever Among 180 patients who were thoroughly studied, they found 14 who showed sensitivity to plantain, an incidence of 7.7 per cent

Concerning the extraction of ragweed, Zoss and his associates⁶⁷ isolated the precipitate produced by the addition of potassium alum to the ordinary watery extract and made the interesting observation that guinea-pigs could be readily sensitized with the preparation One cubic centimeter of the precipitate suspended in an amount of salt solution equal to the original quantity of the ragweed extract was sufficient to sensitize guinea-pigs when injected subcutaneously After twenty-two days the animals were given intravenous doses of the same "aqueous ragweed extract" (which I take to mean the same precipitate suspension) At any rate, all 12 of the animals showed definite symptoms, and 9 which received larger doses died in typical anaphylactic shock When this alum precipitate was used in the routine treatment of patients with hay fever, however, the results were distinctly disappointing and, indeed, not so good as for the control series of patients treated with the usual material

Specific Treatment and Its Results—The treatment of hay fever by giving pollens by mouth, either in the form of the extract or of capsules containing the native pollens mixed with some inert substance like sugar or starch, is under investigation Since 1922, when Touart⁶⁸ treated 6 patients with daily doses of tablets containing pollen, the possibility

63 Wodehouse, R. P. Pollen in Hay Fever, *Torrey* **36** 77, 1936, Pollen Grains in the Identification and Classification of Plants VII The Ranunculaceae, *Bull. Torrey Botan. Club* **63** 495, 1936, Pollen Grains in the Identification and Classification of Plants VIII The Alismataceae, *Am. J. Botany* **23** 535, 1936

64 Stealy, Clair L. The Pollen Content of the Air of San Diego, Calif, *J. Lab. & Clin. Med.* **22** 273, 1936

65 Schonwald, Philipp. Atmospheric Causes of Allergy in Western Washington, *Northwest Med.* **36** 14, 1937

66 Blumstein, G. I., and Tuft, L. Plantain Hay Fever Its Incidence and Importance, *J. A. M. A.* **108** 1500 (May 1) 1937

67 Zoss, A. R., Koch, C. A., and Hirose, R. S. Alum-Ragweed Precipitate Preparation and Clinical Investigation, Preliminary Report, *J. Allergy* **8** 329, 1937

68 Touart, M. D. Hay Fever Desensitization by Ingestion of Pollen Protein, *New York M. J.* **116** 199, 1922

of therapy by mouth has been considered. Bernstein and Kirsner⁶⁹ show that the gastric juice does not alter the extract so far as the skin test fraction is concerned. McGrew⁷⁰ treated 33 patients with diop doses of a 1 per cent extract of grass pollen and found that 29 were improved. More important is the report of Stier and Hollister,⁷¹ who treated 383 patients and found that the results were about the same as for those treated by the regular parenteral method. Most of the patients had hay fever of the tree or grass pollen type.

Whether the successful treatment of patients with hay fever results regularly in a reduction in the size of the cutaneous reaction is always debatable. Baldwin and Glaser⁷² found a reduction in half their patients. The degree of sensitivity of the mucous membrane, however, was always reduced if the patient was clinically improved. It is important, however, that these investigators also observed a few patients who were improved even though the cutaneous reactions remained about the same and a few others who were unimproved in spite of the fact that the cutaneous reactions were reduced in size. Harley⁷³ treated 40 patients who were sensitive to grass pollen, giving a final dose of 100,000 units, and concludes that pollen therapy results in a decrease in the cutaneous reaction whenever a sufficient dose is reached.

Constitutional reactions are still common. Furstenberg and Gay⁷⁴ review the literature carefully in a comprehensive article. Their own series included 907 patients, 45 of whom (4.9 per cent) had one or more major constitutional reactions, whereas only 0.2 per cent of the individual injections administered were accompanied with a general reaction. The results of the prophylactic treatment of 612 patients with hay fever due to ragweed are given in an elaborate table by Clarke and Leopold.⁷⁵ To those who are interested in this subject, it is comforting to have a friend acknowledge publicly that his results also are poor.

69 Bernstein, C, Jr, and Kirsner, J B. Oral Pollen Therapy, *J Allergy* **8** 221, 1937.

70 McGrew, G D. Time and Money Saved in Treatment of Hay Fever. *Mil Surgeon* **80** 371, 1937.

71 Stier, R F E, and Hollister, G. Desensitization by Oral Administration of Pollen Extracts, *Northwest Med* **36** 166, 1937.

72 Baldwin, Louis B, and Glaser, J. Effect of Treatment on Skin and Mucous Membrane Sensitivity and on Reagents in Hay Fever, *J Allergy* **8** 129, 1937.

73 Harley, D. Hay Fever. I. Effect of Pollen Therapy on Skin Reactions, II. Reaction-Inhibiting Substance in Serum of Treated Patients, *J Path & Bact* **44** 589, 1937.

74 Furstenberg, F F, and Gay, L N. The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma. Analysis of the Causative Factors, *Bull Johns Hopkins Hosp* **60** 412, 1937.

75 Clarke, J A, Jr, and Leopold, H C. Prophylactic Treatment for Ragweed Hay Fever, *J Allergy* **8** 560, 1937.

Perennial Vasomotor Rhinitis—Closely related to hay fever is the allergic condition in which the symptoms do not occur at any particular season but come and go throughout the year. Perennial vasomotor rhinitis is often difficult to treat. The cases fall into two groups. In the first group the condition is like hay fever, being dependent on sensitiveness to foreign substances, like orris powder, animals, feathers or some occupational dust with which the patient comes in contact. In the second group the condition is more obscure. Here the cutaneous tests give negative results, and the symptoms are remarkably troublesome. The patients are mostly adults, and there are more women than men. In this particular group a sensitiveness to dust or to food can be excluded by experimental trial, since the symptoms do not change in accordance with changes in the environment or diet. Nash⁷⁶ well says that it is "a disease of civilization." Certainly many of these patients lead sedentary lives. They eat too much, and they exercise not at all. They are too fat, and a number of them obtain relief after attention to their general hygiene. Dean and his co-workers⁷⁷ discuss the group, pointing to possible dietary and endocrine factors, but with not much evidence to throw the theories in or out.

Local treatment with ionization, radium, diathermy and trichloroacetic acid and their results are discussed at length. It is evident that no one method is always successful. As Weille recently explained to me, the cause of the chronic swelling of the mucous membrane is often obscure, but nevertheless the patient suffers from nasal obstruction, frequent sneezing and a troublesome watery discharge from the nose, and these symptoms are severe enough to disturb the general health. Treatment is needed, and a good deal can be done. In giving local treatment, however, one must remember certain principles. First, it is essential that the surface epithelium should be preserved. Second, shrinkage of the turbinates must occur from within the tissue itself, and the object of treatment should be to produce fibrous tissue which will subsequently contract and so make the tissue smaller. Many kinds of treatment will accomplish these ends. Simple cautery of the surface with silver nitrate or with trichloroacetic acid will produce a local area of scar tissue which will be effective for a time. The surface membrane is destroyed by such treatment, but, later it will regenerate, and the symptoms will return. Ionization accomplishes much the same result, but studies of the tissues made before and after the treatment show that the procedure causes a good deal of necrosis in the body of the turbinate and a reac-

76 Nash, C. S. Vasomotor Rhinitis, New York State J. Med. **37** 293, 1937

77 Dean, L. W., Linton, L. D., Smit, H. M., and Dean, L. W., Jr. The Treatment of Allergic Rhinitis, J. A. M. A. **108** 251 (Jan 23) 1937

tion which may be severe. Here, again, the tissue will regenerate later, and so the symptoms will recur. In a recent paper Weille⁷⁸ describes 3 cases to bring out this principle and to elucidate the treatment in the individual case.

Clarke and Rogers⁷⁹ found that the condition occurred in 162 of 2,000 patients with allergy but that of the 162, 50 per cent had eosinophilia and 30 had a family history of allergy. A paper by Spiesman and Arnold⁸⁰ is interesting in this connection. With suitable apparatus they recorded the changes in the temperature of the nasal mucous membrane under various conditions. Under normal circumstances the nasal temperature goes up and down with the temperature of the body as a whole, but in those who are hypersensitive to cold, chilling of the skin will make the nasal temperature rise and external heat will make it fall—as though the nose tried to overcompensate for the reaction of the body. What relation may exist between this sort of hypersensitiveness to cold and the other conditions described vividly by Horton, Brown and Roth,⁸¹ in which exposure to cold may be followed not only by urticaria and angioneurotic edema but by actual circulatory collapse, is hard to say. At any rate, the evidence at hand, or rather the lack of evidence, suggests that further studies of this sort along physiologic lines might be worth while.

Fungi—When a patient declares that his hay fever or his asthma occurs only when he goes to a certain house or sleeps in a certain bed or when, on the other hand, persistent asthma clears promptly and completely when the patient is admitted to the hospital, it is clear that the trouble depends on dusts from which the patient can escape. Many patients give positive reactions to cutaneous tests with house dust and sometimes to extracts of kapok or feathers but may not react to any more definite allergens. What is house dust? Ever since van Leeuwen,⁸² in 1924, described the importance of "miasmata" in the air, many workers have thought about molds as causing asthma. So far, however, the relation between molds and asthma has been proved in only a

78 Weille, F. L. Studies in Allergy. Ionization in Treatment of Hay Fever and Vasomotor Rhinitis, *M. Clin. North America* **21** 613, 1937.

79 Clarke, J. A., Jr., and Rogers, H. L. A Statistical Study of Allergic (Vasomotor Rhinitis), *Arch. Otolaryng.* **25** 124 (Feb.) 1937.

80 Spiesman, E. G., and Arnold, L. Host Susceptibility to Common Colds, *Am. J. Digest. Dis. & Nutrition* **4** 438, 1937.

81 Horton, B. T., Brown, G. E., and Roth, G. M. Hypersensitiveness to Cold with Local and Systemic Manifestations of Histamine-Like Character. Amenability to Treatment, *J. A. M. A.* **107** 1263 (Oct. 17) 1936.

82 van Leeuwen, W. S., Bien, L., and Verekamp, H. Experimentelle allergische Krankheiten, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **40** 552, 1924.

few cases Cadham⁸³ was able to produce asthma by making a patient inhale the dust of infected grain, and then in 1930 came the complete study by Hopkins, Benham and Kesten⁸⁴ concerning their patient whose skin was sensitive to a certain penicillium and who later was thrown into an attack of asthma by inhaling the penicillium spores. There are a few other cases like this, but only a few. A good bibliography is in Rowe's⁸⁵ new book on the subject of clinical allergy. Wittich and Stakman⁸⁶ add a report of another case in which they could demonstrate positive reactions to cutaneous tests with various grain smuts and in which definite asthma developed on exposure to the dust containing these smuts.

In contrast to these proved cases, there is a much larger group of patients who show positive reactions to cutaneous tests with mold extracts, and many of these benefit greatly from corresponding treatment. However, one should hesitate to include their cases in the group of proved cases. Positive reactions to cutaneous tests often occur in normal persons or in patients who have no clinical sensitiveness along with the cutaneous sensitiveness, and, secondly, it is always possible that treatment with mold extracts may do good in some nonspecific manner, just as treatment with vaccines or with a stock extract of house dust may do good in a nonspecific manner. Feinberg's⁸⁷ series of patients showing positive reactions to cutaneous tests and good results from treatment with molds has increased considerably, from 50 in 1935 to 62 in 1936 and now to 90. As he said at a recent symposium on fungi

There are four groups of cases—those who have symptoms from ingestion of fungi, particularly the yeasts and the smuts, the latter including ergot, second, are patients who have an actual infection from molds, third, are those who have a dermatitis from the growth of molds especially the monilia group, and finally, there is a small group of patients who have symptoms from the inhalation of mold spores. These spores come mostly from such species as *alternaria*, *hornodendron*, *aspergillus*, *mucor*, and *penicillium*, all of which belong to the group of imperfect fungi—imperfect because the spores are born naked and not in an enclosed sac which must rupture before the individual spores can be set free.

83 Cadham, F. T. Asthma Due to Grain Rusts, *J. A. M. A.* **83** 27 (Julv 5) 1924

84 Hopkins, J. G., Benham, R. W., and Kesten, B. M. Asthma Due to Fungus, *Alternaria*, *J. A. M. A.* **94** 6 (Jan 4) 1930

85 Rowe, Albert H. Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. Manifestations, Diagnosis and Treatment, Philadelphia, Lea & Febiger, 1937

86 Wittich, F. W., and Stakman, E. C. Case of Respiratory Allergy Due to Inhalation of Grain Smuts, *J. Allergy* **8** 189, 1937

87 Feinberg, S. M. Asthma and Allergic Rhinitis from Molds. Analysis of Ninety Cases, *Journal-Lancet* **57** 87, 1937, Fungi, Symposium at the Association for the Study of Allergy, Atlantic City, N. J., June 8, 1937

Mold spores are given off into the air in enormous quantities, and Feinberg⁸⁸ has traced a curve showing the content of mold spores in the air from day to day. This curve is low during the winter and spring, but in May it begins to rise, reaching its height in July, and then continuing more or less high throughout the remaining summer and early fall, not falling off until after the first frost and often not until after the first snowfall. This curve and the high incidence of mold spores is readily explainable when one understands that molds in nature are concerned with the breakdown of vegetable matter. Dead grass and leaves of all sorts must constantly be removed, and the molds do it. The top soil is full of fungi, and it is easy to see why these fungi flourish during the warm summer and the wet fall months.

In the clinic, at the Massachusetts General Hospital cutaneous tests with extracts of several common molds, made as a routine, have shown positive reactions of various sizes to various molds in various patients, and so far the results are difficult to understand. Fortunately, one particular patient has given an important clue to the problem. This patient is a plant pathologist and is so sensitive to *Cladosporium fulvum* that he cannot enter a greenhouse where tomatoes infected with this mold are growing without having a sudden attack of hay fever and asthma. This man is extremely sensitive to *C. fulvum*, yet he gives no reaction to other strains of the same species. In his case the degree of sensitivity and the degree of specificity are both extreme. Recently, my colleagues and I⁸⁹ saw 3 patients, all professional tomato growers, who also had marked cutaneous sensitivity to extracts of *C. fulvum*. Other strains produced no reaction in them. The mold allergy was highly specific. The important results obtained in these cases indicate that the difficulties in the study of hypersensitiveness to fungi depend on a high degree of specificity among the strains of molds which has not been recognized hitherto. The lead provided by this observation is being followed enthusiastically.

ASTHMA

Complications of Asthma—The complications of asthma, especially the development of subcutaneous emphysema and spontaneous pneumothorax, have had more than the usual attention during the past year. The literature was well reviewed by Sheldon and Robinson⁹⁰ in 1936.

88 Feinberg, S. M., and Little, Harold T. Studies on the Relation of Microorganisms to Allergy. III. A Year's Survey of Daily Mold Spore Content of the Air, *J. Allergy* **7** 149, 1936.

89 Rackemann, Francis M., Randolph, T. G., and Guba, E. F. Specificity in Mold Allergy, to be published.

90 Sheldon, John M., and Robinson, William D. Subcutaneous Emphysema in Asthma, *J. A. M. A.* **107** 1884 (Dec. 5) 1936.

Reports of 3 new cases are added by Kirsner,⁹¹ by Bridge⁹² and by Faulkner and Wagner⁹³. The state of the heart and the general diagnosis of cardiac asthma always present difficult problems. Colton and Ziskin⁹⁴ made a study of the heart in 84 cases of asthma but could not find that it was greatly involved. Electrocardiography gave some evidence that strain of the right ventricle, with some myocardial damage, occurs as the asthma progresses and emphysema ensues. Swineford and Magruder⁹⁵ present a sensible and plausible analysis of cardiac asthma, indicating that the diagnosis always means two diseases—first, heart disease and, second, asthma, that the wheeze itself is enough to indicate asthma and that in most cases this wheeze antedates the evidence of cardiac disturbance. In connection with the pathologic picture, physicians must not overlook periarteritis nodosa, which, according to Ehrstrom,⁹⁶ may be a complication. I have also seen 1 patient with this complication.

Asthma and the Nose and Throat—Kelley⁹⁷ found that hyperplastic involvement of the nasal sinuses as a part of the clinical picture of asthma was even more common than is clinically supposed. He found that it occurred in 89 of 100 cases. It is interesting, however, that of the 11 "negative" cases, asthma had existed for over ten years in 4 and for over five years in 6. The point is that changes in the sinuses are not an obligatory complication of asthma.

Asthma is often treated primarily by the otolaryngologist. Fox and Harned⁹⁸ reviewed their material and present the results obtained in 150 patients treated locally, comparing them with those obtained in another 150 patients treated by "medical methods." The surgical procedures seemed to be effective according as the surgical operation

91 Kirsner, J. B. Subcutaneous Emphysema in Bronchial Asthma. Report of a Case, J. A. M. A. **108** 2020 (June 12) 1937.

92 Bridge, F. Subcutaneous Emphysema in Asthma, J. A. M. A. **108** 492 (Feb. 6) 1937.

93 Faulkner, William B., Jr., and Wagner, R. J. Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic. Report of Case with Bronchoscopic Findings, J. Allergy **8** 267, 1937.

94 Colton, W. A., and Ziskin, T. The Heart in Bronchial Asthma, J. Allergy **8** 347, 1937.

95 Swineford, Oscar, Jr., and Magruder, R. G. Asthma in Heart Disease. A Clinical Study with Especial Reference to Cardiac Asthma, South M. J. **30** 829, 1937.

96 Ehrstrom, E. Irreversible Allergic Changes in Blood Vessels. Glomerulonephritis, Periarteritis Nodosa and Rheumatic Arteritis, Finska lak-sallsk. handl. **80** 332, 1937.

97 Kelley, S. F. Incidence of Sinusitis and Nasal Polyps in Bronchial Asthma. Laryngoscope **46** 692, 1936.

98 Fox, N., and Harned, J. W. Treatment of Asthmatic Patient in Otolaryngologic Practice, Arch. Otolaryng. **25** 393 (April) 1937.

was extensive. Figures for the results of different operations varied from 32 to 60 per cent "cured"—the duration of "cure" not being stated. In contrast with these figures, the "medical" patients had all sorts of treatment, with such procedures as the injection of iodized poppy-seed oil 40 per cent, vaccines, extracts of nasal tissue and serum from patients who were doing well postoperatively, yet none of them was greatly benefited. The authors conclude, of course, that surgical is better than medical treatment. The trouble with this report is that asthma varies so widely in duration, kind and cause that it is hardly fair to compare results in numbers of cases without knowing more about them.

Somewhat related is a fairly new idea that asthma, like bronchiectasis, can be treated by intratracheal injections of iodized oil. Mandelbaum⁹⁹ has studied the literature carefully and has compiled from it a study of 1,000 cases, to which he adds 114 cases of his own. He is wise to emphasize the importance of excluding all the common causes of asthma before the intratracheal treatment is undertaken. Obviously, this treatment should be a procedure of last resort. On the other hand, the treatment evidently does little immediate harm, and it is interesting to observe how many treatments have been given and how much oil has been injected in certain cases. In Mandelbaum's series as many as eighty-four injections were sometimes necessary in 1 case before the asthma was relieved, and in his series the average number of injections was thirty-seven. The average amount of oil used was 684 cc—usually these treatments consisted of giving 20 cc at a time. The average interval between doses was six days, and the longest period of treatment was two years and four months. The results in the 1,000 cases quoted were: complete relief in 24 per cent, marked relief in 34 per cent, slight relief in 17 per cent and no relief in 25 per cent. There were 2 deaths, which were presumably dependent on hypersensitiveness to iodine. More recently Crip and Hampsey¹⁰⁰ observed 40 patients with asthma treated with iodized oil, but only 4 were relieved. In 17 cases the treatment was a complete failure. It is interesting to compare these figures with those derived from a similar large series of cases which I¹⁰¹ reported in 1927. This group comprised patients with

99 Mandelbaum, M. J. Asthma. Treatment by Intratracheal Injection of Iodized Oil, with an Analysis of One Thousand Compiled Cases, Including One Hundred and Fourteen Newly Reported Cases, *M. Clin. North America* **20** 907 1936.

100 Crip, Leo H., and Hampsey, J. W. Therapeutic Value of Iodized Oil in Bronchial Asthma, *J. Allergy* **9** 23, 1937.

101 Rackemann, Francis M. Studies in Asthma. I. A Clinical Survey of One Thousand and Seventy-Four Patients with Asthma Followed for Two Years, *J. Lab. & Clin. Med.* **12** 1185, 1927.

asthma of every sort, and it included a few children. The gross results were "cured," 20 per cent, improved, 50 per cent, same, 20 per cent, and dead, 10 per cent. Evidently the ultimate outcome in the treatment of asthma is, by and large, fairly constant.

The pathologic picture of asthma, as observed in 137 patients who died with or because of asthma, is described in an excellent article by Lamson and Butt¹⁰². They found that in cases of death from asthma itself the formation of mucous plugs in the bronchi was observed as a characteristic at autopsy. Many of the patients died with asthma rather than because of asthma, and the fact is emphasized. Some of them died within four years after the onset of symptoms.

ECZEMA

Allergic Eczema—Allergic eczema, with lesions in a characteristic distribution on the face, neck, elbows and knees, is typical of allergy ("atopy"). Its mechanism, including its clinical relation to specific foods and dusts, the obtaining of positive reactions to cutaneous tests and the presence of reagins in the blood, is similar to that of hay fever and asthma. This fact is being recognized more and more. The condition varies with the seasons of the year, with changes of environment and often with changes in dietary. It is obvious that the cause of the disorder is something which reaches the skin from the blood stream underneath. Sulzberger's¹⁰³ papers describe the condition and the classification clearly.

Contact dermatitis is somewhat related, but here the lesions are limited to exposed surfaces, and the cause of the disorder reaches the skin directly. Poison ivy is in this group, and the recent studies by Straus¹⁰⁴ on poison ivy in animals are of particular interest. Using a 13 per cent acetone extract of dried poison ivy leaves, Straus was able to sensitize guinea-pigs by applying the material to the skin as in a patch test, leaving the application in place for forty-eight hours. Removal of the patch gave no visible reaction, but when, seven or ten days later, a similar patch was applied to another site, typical dermatitis developed in forty-eight hours. Straus observed that sensitization with poison ivy resulted also in a slight sensitization to poison oak. There is a common antigenic principle in the two. The later paper is more important because it points directly to the manner in which hypersensitiveness

102 Lamson, R. W., and Butt, E. M. Fatal "Asthma." Clinical and Pathologic Consideration of One Hundred and Eighty-Seven Cases, *J. A. M. A.* **108** 1843 (May 29) 1937.

103 Sulzberger, M. B. Remarks on Definitions and Classification in Certain Forms of Dermatologic Allergy, *New England J. Med.* **215** 330, 1936.

104 Straus, H. W. Studies in Experimental Hypersensitiveness in the Rhesus Monkey. I. Active Sensitization with Poison Ivy, *J. Immunol.* **32** 241, 1937.

spreads to all the skin. Straus¹⁰⁵ removed a ring of skin from the upper part of the arm of a monkey and then applied his original sensitizing patch to the skin below the ring. Two weeks later tests showed that below the ring, sensitiveness of the skin of the arm was plainly evident but patches placed on the skin in other parts of the body always gave negative results. This other skin had not been sensitized, and so the authors claim properly that cutaneous sensitiveness spreads not by the blood or perhaps by the lymph but apparently by some method of transmission through the skin itself.

The specific therapy of poison ivy has been improved. Sharlit and Newman¹⁰⁶ describe the importance of making extracts with absolute alcohol, saying that the dermatogen is soluble best in this diluent. Sixty-three of the 74 patients treated obtained complete relief from their symptoms on the fourth day. Caulfeild¹⁰⁷ has a similar idea, for he says that the active part of the poison ivy plant is soluble best in ether and the ether extract is readily soluble in corn oil. Treatment by intramuscular injections of his oleo-antigen produced marked clinical improvement, even though the degree of cutaneous sensitiveness was not greatly reduced.

The erysipelas-like eruption which sometimes complicates fungous infections of the feet has been studied by two groups of workers, Traub and Tolmach¹⁰⁸ and Sulzberger and his associates¹⁰⁹. The fact that the fungous disease can of itself cause a severe constitutional reaction, with localized lymphangitis and enlargement of the inguinal lymph nodes, is enough to establish the diagnosis and to allay fears concerning an acute streptococcic infection, which the condition simulates so closely.

DRUG ALLERGY

Knowledge of drug allergy is advanced chiefly by the increasing number of reports of new cases. Weber¹¹⁰ performs an extraordinary

105 Straus, H. W., and Coca, Arthur F. Studies in Experimental Hypersensitiveness in the Rhesus Monkey. III. On the Manner of Development of the Hypersensitiveness in Contact Dermatitis, *J. Immunol.* **33** 215, 1937.

106 Sharlit, H., and Newman, B. A. Specific Therapy in Rhus Dermatitis, *New York State J. Med.* **37** 61, 1937.

107 Caulfeild, A. H. W. Prevention of Poison Ivy Dermatitis by the Intramuscular Injection of "Rholigen" (Rhus Tox., Oleo-Antigen), *Canad. M. A. J.* **37** 18, 1937.

108 Traub, E. F., and Tolmach, J. A. An Erysipelas-Like Eruption Complicating Dermatophytosis, *J. A. M. A.* **108** 2187 (June 26) 1937.

109 Sulzberger, M. B., Rostenberg, A., and Goetze, D. Recurrent Erysipelas-Like Manifestations of the Legs. Their Relationship to Fungous Infections of the Feet, *J. A. M. A.* **108** 2189 (June 26) 1937.

110 Weber, L. F. External Causes of Dermatitis. A List of Irritants, *Arch. Dermat. & Syph.* **35** 129 (Jan.) 1937.

service by publishing a list of important irritants, arranged first by alphabet and second by the occupations in which they occur. Some of the chemicals produce irritation in normal as well as in sensitive persons, but nevertheless the list with its two hundred and forty-five references makes a useful reference work.

Dyes remain the important source of trouble. Goodman and Sulzberger¹¹¹ report 25 cases of sensitivity to the dyes in clothing, especially in women's dresses. All colors were incriminated, but whereas there were thirty positive reactions to patch tests with black materials, there were only nine with brown, eight with red, six with blue, five with green and two with orange. One patient reacted to thirteen dress materials at the same time. Shoe dermatitis and sock dermatitis are not uncommon. Traub, Gordon and Van Dyke,¹¹² in a report on dermatitis from the dyes used in coloring fruits, described two cases in which the yellow dye used on oranges was the principal offender. Vallery-Radot¹¹³ publishes another paper on cutaneous disease in furriers caused by paraphenylenediamine. Downing¹¹⁴ had a patient who was sensitive to phenylhydrazine. Crip¹¹⁵ saw a patient who was so sensitive to metaphen that the painting of his skin with this drug resulted in a massive swelling of his arm and later in asthma. Baker and Brunsting¹¹⁶ call attention to sulfocyanates, and Miller and O'Donnell¹¹⁷ observed collapse and shock after the third dose of tryparsamide. Seymour¹¹⁸ reviewed the literature on sensitivity to iodine and found reports of 14 cases of extensive generalized eruptions 7 of which were fatal. One patient had severe reactions after each treatment for pneumothorax, and finally the disorder was traced to

111 Goodman, J, and Sulzberger, M. B. Acquired Specific Hypersensitivity and Simple Chemicals. I. Non Industrial Dye Sensitivity, read at the meeting of the Association for the Study of Allergy, Atlantic City, N. J., June 8, 1937.

112 Traub, E. F., Gordon, R. E., and Van Dyke, L. S. Dermatitis from Dyed and Otherwise Treated Citrus Fruits. Report of Two Cases, *J. A. M. A.* **108** 872 (March 13) 1937.

113 Vallery-Radot, P. Manifestations asthmatiques chez les fourreurs dues a une sensibilisation a la paraphenylenediamine, *Bull. Acad. de med., Paris* **115** 773, 1936.

114 Downing, J. G. Dermatitis from Phenylhydrazine Compounds. Report of Case, *New England J. Med.* **216** 240, 1937.

115 Crip, Leo H. Allergy to Dyes. Contact Dermatitis from Easter Egg Dye, Asthma and Urticaria from Metaphen, *J. A. M. A.* **108** 1169 (April 3) 1936.

116 Baker, T. W., and Brunsting, L. A. Dermatitis Medicamentosa Resulting from Administration of Sulfocyanates in Treatment of Hypertension, *J. A. M. A.* **108** 549 (Feb. 13) 1937.

117 Miller, J. K., and O'Donnell, H. J. Sensitivity to Tryparsamide, *Arch. Dermat. & Syph.* **35** 264 (Feb.) 1937.

118 Seymour, W. B., Jr. Poisoning from Cutaneous Application of Iodine. A Rare Aspect of Its Toxicologic Properties, *Arch. Int. Med.* **59** 952 (June) 1937.

the extensive rash which followed the painting of the skin with iodine and which was accompanied with nausea and collapse—a serious disturbance. Boros¹¹⁹ had a patient in whom jaundice developed after large doses of cinchophen. Of more practical interest is the report of Prickman and Buchstein,¹²⁰ who present a careful study of sensitiveness to acetylsalicylic acid. Reports of 33 cases were found in the literature and 62 more cases were recognized at the Mayo Clinic. In them the taking of acetylsalicylic acid had resulted in the following reactions: asthma in 38 (61.2 per cent), urticaria in 12 (19.3 per cent), vasomotor rhinitis in 3 (4.8 per cent) and gastro-intestinal symptoms in only 3 (4.8 per cent). So far there is no good test for sensitivity to acetylsalicylic acid except the homely method of trial and error. Fixed drug eruptions are described by Abramowitz and Noun.¹²¹ Typical bullous lesions, usually around the mouth and genitals, may develop after the taking of any one of a long list of drugs. Why the lesions should be localized and always occur in the same spot is hard to say. Evidently the degree of sensitiveness can be greater in certain areas of the skin than in others.

MISCELLANEOUS MANIFESTATIONS OF ALLERGY

The list of manifestations of allergy becomes longer from year to year, partly because the members of the medical profession are becoming "allergy conscious" and so are learning to think of allergy when the cause of some sudden disturbance is otherwise unknown and because in many cases this point of view is justified, especially when there is a story of previous contact with the particular substance under suspicion. In most of the cases of agranulocytosis, for example, the patient tells a story of having taken aminopyrine or some other drug previously and without trouble. It was the second course of treatment begun recently which caused the upset. Three recent articles describe cases in which thrombopenia and purpura seemed due to allergy as follows. Squier and Madison¹²² found 6 patients who improved after the elimination of certain foods, and in all cases the ingestion of these foods caused an occurrence of the purpura. Beiglböck's¹²³ patient

119 Boros, Edwin. Hay Fever and Asthma During and After Jaundice. Ascites Due to Cinchophen Poisoning, *J. A. M. A.* **109** 113 (July 10) 1937.

120 Prickman, L. E., and Buchstein, H. F. Hypersensitivity to Acetylsalicylic Acid (Aspirin), *J. A. M. A.* **108** 445 (Feb. 6) 1937.

121 Abramowitz, E. W., and Noun, M. H. Fixed Drug Eruptions, *Arch. Dermat. & Syph.* **35** 875 (May) 1937.

122 Squier, T. L., and Madison, F. W. Thrombocytopenic Purpura Due to Food Allergy, *J. Allergy* **8** 143, 1937.

123 Beiglböck, W. Ein Fall von thrombopenischer Purpura bei echter Chininüberempfindlichkeit, *Ztschr. f. klin. Med.* **131** 308, 1937.

when tested with quinine gave an extraordinary reaction, with tremendous local swelling and hemorrhage appearing in half an hour. Vomiting, chills, fever and cyanosis occurred, but there was ultimate recovery. Fernan-Nuñez¹²⁴ declares that hemoglobinuric fever may be an allergic phenomenon associated perhaps with infestation by a certain plasmodium. In sensitive persons a minute intracutaneous injection of a suspension of the plasmodium treated with solution of formaldehyde produced a positive cutaneous reaction.

Certain diseases of the eye may depend on allergy. Conjunctivitis is the most important and may be due to some substance contained in cosmetics or in preparations like henna and "lash lure." Unger¹²⁵ reviews the recent literature and describes the evidence for allergy as a cause of vernal catarrh. Vaughan and Sullivan¹²⁶ have evidence that allergy may play a part in essential hypertension. By means of a carefully taken history, cutaneous tests and the leukopenic index, dietary factors were found in certain cases which did seem to have a direct relation to the height of the blood pressure, which fell markedly when the different foods were removed. Gay,¹²⁷ of St. Louis, also comments on food allergy in cases of essential hypertension and in paroxysmal tachycardia. Cutaneous tests were not common in his series, but, as he writes, "it is more important to discover what a food does to the organism as a whole than to discover what the extract of that food does to an isolated portion of the skin." Essential dysmenorrhea may be allergic, according to Schwartz and Smith,¹²⁸ who made a study of 35 patients and by "allergic management" brought relief to 29 patients, which was complete in 20.

Only a relatively few of the papers published on allergy and its manifestations during the year have been mentioned in this review. As before, I have picked out only those papers and subjects which seemed to have a bearing on the aspects of allergy which interested me. A line must be drawn somewhere simply on account of limitation of space, and there is no doubt that many good papers have been left out. The literature has increased to the point that any complete review of the papers published even in one year would require not an article

124 Fernan-Nuñez, M. Hemoglobinuric Fever. Is It an Allergic Phenomenon? *Am J Trop Med* **16** 563, 1936.

125 Unger, Leon. Allergy of the Eye, Ear, Nose and Throat, *Illinois M J* **71** 47, 1937.

126 Vaughan, W. T., and Sullivan, C. J. On the Possibility of an Allergic Factor in Essential Hypertension, *J Allergy* **8** 573, 1937.

127 Gay, L. P. Food Allergy in Internal Medicine, with Special Reference to Paroxysmal Tachycardia and Essential Hypertension, *J Missouri State M A* **34** 332, 1937.

128 Schwartz, O. H., and Smith, D. R. Essential Dysmenorrhoea and Allergy, *Am J Obst & Gynec* **33** 331, 1937.

but a whole book. Certain topics, like acetylcholine, the increasing appreciation that the value of cutaneous tests is limited, the nature and treatment of perennial vasomotor rhinitis, fungous allergy and the recent evidence of the great specificity among fungi, and certain new treatments for intractable asthma seem to represent the important contributions made during the year. I must emphasize that great selection has been necessary and that many readers will be obliged to look elsewhere for complete information on some of the special aspects of the tremendous and fascinating problems presented by clinical allergy.

263 Beacon Street

Book Reviews

Cancer and Diet By Frederick L Hoffman Price, \$5 Pp 767 Baltimore
Williams & Wilkins Company, 1937

This volume of 767 pages represents the result of years of work. Much of the expense of the study and of the publication of the book was borne by Mr Fels, of Philadelphia. Unfortunately, the work was carried on in such a way that the reviewer, at least, cannot be sure of what it all means. At first glance it seems as if something definite could have been learned about cancer and its relation to diet if a careful statistician, well trained to avoid the many pitfalls that lie in his path, were to have traveled about the world correlating the incidence of various types of cancer with the remarkable differences in dietary habits which are to be found in different lands. But unfortunately, even then it might be impossible to draw conclusions because, as every pathologist knows, whenever a group of older persons come to necropsy a large number of cancers are always found the presence of which was not suspected during life. Obviously, then, all figures purporting to give the incidence of carcinoma in any part of the world must be far from correct. Much depends also on the average age of the persons studied. Hence a missionary starting practice in China or Korea may for a time see so little cancer that he will be tempted to write an article on the anticarcinogenic effects of a vegetarian diet, but gradually as he gains the confidence of the people, some of the older men and women are induced by their children to consult the "foreign devil," and then plenty of cancer is found.

The statistically minded and trained will be astounded to find Mr Hoffman saying in his introduction that he has "avoided the use of mathematics as entirely uncalled for and most likely to prove confusing to the nonmathematical mind." But why should not the book have been written primarily for mathematically minded, competent statisticians and written so that they could be convinced of something or other by the evidence presented? When will men learn that it is a sheer waste of time to convince people who are not competent to judge as to whether or not the work was good or bad?

The feature of this book perhaps most disturbing to a physician who knows the literature and something about the men who have written it is the author's apparent naive belief that whatever is to be found in an old textbook or an old medical journal is gospel truth. For instance, in discussing carcinoma of the stomach not only does Hoffman quote cheerfully from Soltau Fenwick's ancient book, which was antiquated even when it was published a generation or more ago, but he seems willing to assign this quotation the same value as he might give to the statement of a man who in recent years has carefully analyzed several hundred case records.

Worse yet is the author's uncritical handling of his data and his apparent lack of all interest as to how they were obtained. To him cancer seems to be cancer, no matter whether it is sarcoma of the thumb in a boy of 18 or carcinoma of the rectum in a man of 70. Furthermore, it appears to be all the same to him whether a man with carcinoma has a small nodule which has not yet affected his health in any visible way or whether it is as big as the hand and has reduced the poor victim to skin and bones.

For instance, on page 505 the author, while apparently trying to find out what etiologic relation there is between constipation and cancer, states that the proportion of male patients with cancer having no daily bowel movement was 116 per cent against 84 per cent for the male control patients without cancer. But what can this prove? One would first need to know in what percentage of cases the carcinoma was in the colon or at the pylorus, where it could produce constipation, and more important yet, one would need to know in how many cases constipation

preceded the onset of the carcinoma? In how many was it simply the result of the weakness, starvation and inactivity produced by the carcinoma? And then what is constipation? Many persons who would classify themselves as constipated have really had diarrhea for years, owing to the taking of a daily purgative. So far as one can tell from the book, such questions bother Hoffman not a bit.

He goes on to state that the best discussion on intestinal stasis in relation to cancer with which he is familiar is in the book by Jordan. This is disturbing, because it would probably be hard to find any American roentgenologist who would have a good word to say for this now-forgotten book which Jordan wrote years ago to back up the views of his co-worker Sir Arbuthnot Lane. Strangely, also, Hoffman still feels great admiration for Lane as the "foremost authority on intestinal stasis." One wonders where in America today he could find any eminent or well posted physician who would join with him in eulogy of this erstwhile booster for Fleischmann's yeast.

And so it goes, until the busy physician is compelled to turn away with the feeling that if anything of value can come out of such loosely gathered statistics—such averaging up of cats, dogs and giraffes, he does not have the time to search for it.

Morphologische und tierexperimentelle Studien über dem Schleimhautrelief der Magen-Darmkanals By Stenn Grettve. Acta Radiologica. Price, 10 kronor. Stockholm. P. A. Norstedt & Soner, 1936.

The increasing importance of the relief topography of the mucosa in the refinement of gastro-intestinal roentgenography is well recognized. The constitution of the elements of the relief topography has been made the subject of an exhaustive morphologic and experimental investigation by Stenn Grettve at the Karoline Institute in Stockholm. He has made a comprehensive survey of the literature of the past hundred years and places special emphasis on the work of Forssell, who emphasized the plasticity of the mucosa and the lack of preformed anatomic folds.

Grettve demonstrates that the thickening of the muscularis mucosae at the height of a fold is an active process of contraction. The mucosal capacity for enlargement in response to intraluminal changes in pressure includes the ability of the low relief to alter its surface. Thus when the stomach is full the crypts are widened and flattened, and it is possible to see the openings of the glands at the bottom of the crypts. These changes are illustrated clearly.

Combining submucosal injection of saline solution with arterial injection, the author obtained a clear reconstruction of the vascular arrangement in the gastric submucosa and inner mucosa, which he describes in detail. He concludes that the vascular supply is a factor but does not determine the changes in the form of the submucosa.

A special apparatus was devised to isolate portions of the stomach of a living animal so as to permit a study of the mucosal reaction to physical and pharmacologic agents and to changes such as stretching or contraction of the muscularis propria. The mucosa is a soft, pliable membrane, possessing a marked capacity to resist mechanical influences. Passively induced physical changes are temporary and are readily followed by a return to the original pattern, which has a certain configuration typical of the species but varies in minor detail from time to time and from person to person. Locally applied epinephrine causes passively induced changes to endure longer. It causes higher, softer, smaller and more numerous folds, with increased sinuosity. Pilocarpine hydrochloride applied locally creates lower, broader and fewer folds. Intravenous administration was less effective in both cases. The muscularis mucosae is considered the site of these changes.

Confirmation of previous experiments concerning the special adaptability of the mucosal surface to solid particles is established. The direction that high folds assume under the influence of contractions of the outer muscle wall follows obvious physical laws, i. e., it is at right angles to the axis of contraction.

A quantitative analysis was made of the water content of the wall of the stomach. This was greater in the full than in the empty stomach. There was

more than twice the content of water in the folded portion as in the fold-free portion. The water content of the mucosa and submucosa combined was found to be higher than that of the muscularis.

Finally the author exhibits the distribution of the capillaries and finer arteries in the mucosal surface.

For one set of experiments anesthetized cats and rats were given histamine intracardially, and before death the portal vein was clamped, thus producing the maximum exhibition of the capillaries. The sections showed large numbers of distended capillaries in the mucosa but only sparse filling of the submucosal capillaries. The serosal capillaries were numerous and well filled. The sites of the microscopic and low relief showed marked capillary vascularity compared with the furrows between the relief structures. The author believes that the surface capillary network may contribute to the formation of the microscopic appearance and low relief.

In conclusion, the author states that the mucosa through its intrinsic musculature plays an important role in the form and function of the digestive surface of the gastro-intestinal canal. There is an active process of mucosal accommodation, partly to the surface and form of the outer muscle wall and partly to the intraluminal contents. To a lesser extent there is passive wrinkling induced by contraction of the outer wall. All the processes serve to meet the varying needs of digestion.

Materia Medica, Toxicology and Pharmacognosy By William Mansfield, A M, Pharm D, Professor of Materia Medica and Toxicology, Union University. Price, \$6.75. Pp 707, with 202 illustrations. St Louis C V Mosby Company, 1937.

This book has individuality and a good deal of charm. As is stated in the preface, it is a textbook and reference work on the therapeutics, toxicology, pharmacognosy and posology of the official drugs of "The Pharmacopoeia of the United States of America" and the "National Formulary."

It is an interesting combination—in many ways an old-fashioned herbal walking hand in hand with a modern textbook. One sees pictures of homely herbs and flowers, like thyme, roses or foxglove, and learns how as the years have passed they have come to be used by medical men as thymol, pills of aloe and mastic or tincture of digitalis. The illustrations from the herbals are not perfect but are sufficiently good and reasonably clear. For the unknowing there are short chapters that deal with the elements of botany which every physician should know and also a simple glossary whereby an ignoramus can quickly become fascinated by a new and pleasant language and wish to learn more of it.

The toxicologic portion of the volume is more orthodox. Particular emphasis is laid on the point of view that any drug is a medicine only so long as it produces a therapeutic effect and that it becomes a poison when the amount taken causes sickness, disease or death. Considerable space is occupied in describing the toxic manifestations of many drugs and the procedures to be employed in offsetting them.

Finally is listed the dosage of drugs given in "The Pharmacopoeia" and in the "National Formulary," grouped first from lowest to highest dose and later alphabetically. A good index completes the work.

One is inclined to agree with the author. A volume of this character should indeed prove useful to physicians, pharmacists, and students of medicine, pharmacy and nursing.

Clinical Roentgenology of the Cardiovascular System By Hugo Roesler, M D. Price, \$7.50. Pp 343, with 199 illustrations. Springfield, Ill. Charles C Thomas, Publisher, 1937.

Intensive investigations have created gaps—unavoidable by virtue of their inherent trends—between varied and yet related fields of medical science. In the attempt to bridge one of these gaps, the clinician and the roentgenologist have built up a loose form of cooperation, each borrowing from the knowledge and

experience of the other. "Clinical Roentgenology of the Cardiovascular System" offers to the cardiologist everything that its title implies. The author, fundamentally a clinical physiologist and thoroughly conversant with the mechanism of cardiac symptoms and signs, has made a roentgenologic study of the cardiovascular system, with all the fundamentals of normal and pathologic physiology projected into his observations. That is, he has borrowed directly from the specialized branches of medicine and not from the specialist in interpreting them.

Considerable attention is given to the description of correct roentgenologic technic, including orthodiagraphy and kymography. The difficulties encountered and the mathematical considerations involved in the determination of the size and volume of the heart are fully discussed. The book includes a chapter covering the important details of arteriography. The descriptive picture is clear, and the objective findings of fluoroscopy are correlated with the phenomena responsible for the clinical picture.

The differential diagnosis of individual lesions under their separate headings has called for a certain degree of repetition. This, however, the reader will find more helpful than cumbersome. Illustrations are well selected and adequately explained.

Quelques vérités premières (ou soi-disant telles) sur les maladies du foie. By Noel Bressinger. Price, 24 francs. Pp 82. Paris: Masson & Cie, 1936.

This short presentation of "some of the primary truths about hepatic disease" consists of many present day clinical axioms, based mainly on the author's experience. The axioms are, as axioms should be, brief and to the point. The monograph is devoid of any discussion. It is limited to considerations that are accepted today as truths. As stated by Bressinger, the truths of today may be the errors of tomorrow.

The author includes in the presentation the examination of the patient, functional disturbances of the liver, organic hepatic disease, methods of roentgenologic and biliary study and treatment of hepatic disease. There is a consideration of the various clinical aspects of hepatic disease. For instance, cirrhosis of the liver is presented as to etiology, symptoms, complications, prognosis and treatment, axiomatic statements being made for each phase of the disease. The chapter on treatment is divided into two parts: first, "that which should be done" and, second, "that which should not be done." Dogmatic statements are briefly made from the medical and surgical points of view.

This interesting monograph contains many salient clinical facts which are dogmatically stated as the accepted truths of today. Not only is the monograph interesting and instructive to those who are seeking information about hepatic disease, but it is interesting and entertaining to those who are well versed in the subject. The reviewer recommends this monograph to all physicians who have a few minutes to spare for interesting and instructive reading.

The Clinical Use of Digitalis. By Drew Luten, M.D., Associate Professor of Clinical Medicine, the Washington University School of Medicine, and Physician to the Barnes Hospital, St. Louis. Price, \$3.50. Pp 226. Springfield, Ill. Charles C. Thomas, Publisher, 1936.

It is the opinion of the reviewer that this book is one of the finest to be found at the present time on the subject of digitalis. It is primarily a study of the drug from the clinical standpoint, and it is a well organized and well written summary of most of the important contributions to the subject during the past ten years. It is not surprising that throughout the book there are frequent delightful references to the history of digitalis and to Withering's cases.

The first chapters are concerned with the pharmacologic action of digitalis in its effect on the ventricular muscle and on the conduction tissues, and they lay the background for the now generally accepted opinion that the therapeutic efficiency of digitalis results from the action of the drug on the ventricular muscle and that

the improvement in cardiac function takes place not at the expense of increasing the work of the heart but by lessening its requirement for energy

The clinical discussion of the indications, dosage, administration, contraindications and dangers of the drug, which comprises the main portion of the volume, is in line with the general authoritative opinion of the day, in which there is but little disagreement. In spite of this uniformity of opinion, digitalis remains a drug which, perhaps more than any other, is most frequently misused. Physicians in general practice as well as those whose interest is primarily in cardiology will find much helpful information in this splendid volume.

Lehrbuch der roentgenologischen Differentialdiagnostik der Erkrankungen der Bauchorgane By Werner Teschendorf, M.D., Chief Physician of the Radiologic Institute, General Hospital, Cologne. Price, 42 marks, bound, 44 marks. Pp 477, with 929 illustrations. Leipzig: Georg Thieme, 1937.

To the roentgenologist who is keenly interested in studies of the alimentary canal and abdominal organs every new book on the subject is a new-found treasure. It is true that there are already many texts and all must be essentially similar, yet all are more or less different in point of view, expression, illustration and emphasis on specific items, and these differences give value to each individual text. These considerations apply fittingly to Teschendorf's volume. Lesions in the three portions of the stomach—cardia, media and pylorus—are described separately. Adequate demonstration of the internal relief is given the emphasis that it deserves. Diseases of the small and the large bowel, pancreas, spleen, liver, gallbladder, kidney, ureter and bladder are all well covered. The text is succinct, the illustrations are extraordinarily clear. Like all books, this one is not beyond criticism. For example, it presents excellent illustrations of hypertrophy of the pyloric muscle, but the conical indentation of the bulbar base and the elongated, indented canal, which are characteristic of the disorder, are not mentioned. However, that is a small fault that is more than offset by the general excellence of the book. To the reviewer the most striking feature of the volume is the extensive and thorough description of the stomach after operation, with diagrams of all standard operations. This chapter alone would make the book worth while.

CORRECTION

The legend for chart 6 in the article by Drs. Chester S. Keefer, Franz J. Ingelfinger and Wesley W. Spink entitled "Significance of Hemolytic Streptococcic Bacteremia. A Study of Two Hundred and Forty-Six Patients," which appeared in the December issue (*ARCH. INT. MED.* 60:1084, 1937), should read:

"Temperatures of patients with hemolytic streptococcic bacteremia for whom culture of the blood was made. The blood was cleared promptly in all but 2 patients without abscess formation, and recovery followed. The arrows indicate the time of incision of an abscess."

CORRECTION

"Hydatid Disease. Clinical Laboratory and Roentgenographic Observations." M. F. Godfrey, M.D. (*ARCH. INT. MED.* 60:783, 1937).

On page 789, in the second line under "Characteristics of Hydatid Elements," the sodium chloride content of the fluid should have been given as 0.6 per cent instead of 6 per cent.

ARCHIVES of INTERNAL MEDICINE

VOLUME 61

FEBRUARY 1938

NUMBER 2

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FATAL RHEUMATIC FEVER

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We present in this report clinical observations on the fatal course of rheumatic fever and its sequelae in 306 young patients. Our purpose is twofold. First, there are important aspects of the natural course of the disease which are best displayed by this special group, and, second, certain clinical features which characterize the disease in its more severe form are not generally recognized as important manifestations of rheumatic fever. The significance of these less well recognized manifestations becomes increasingly evident from a consideration of these fatalities.

MATERIAL

The material dealt with is in some respects unusual. During the past sixteen years (since 1921) approximately 1,500 children and adolescents under the age of 21 years have received prolonged care in bed at the House of the Good Samaritan during the course of active rheumatic fever and chorea. The subsequent course of these patients has been followed by frequent examinations and, when necessary, by readmission of the patients to the hospital. The present status of this large group is known. The 306 patients who are the subject of this report constitute those who have died during the course of the study. We are especially concerned however, with the 250 fatalities directly attributable to rheumatic fever.

Although it is not our purpose to discuss these fatal cases in relation to the entire clinical group, it is of some interest to note at this time that the first 1,000 of the total of 1,500 patients have now been observed for an average period of more than ten years. The present status of this special group is as follows. Of these 1,000 patients, 310 have no demonstrable cardiac damage, 426 have varying degrees of residual rheumatic heart disease, 243 are dead (and comprise the major part of the present study) and finally there remain 21 patients whose present status is unknown. We are convinced that conclusions based on this and similar "average" (and hence incomplete) after-history studies of the course of a disease as notoriously variable as is rheumatic fever are unreliable other than as an indication,

From the House of the Good Samaritan

The expenses of this study have been defrayed by a grant from the Commonwealth Fund

Presented at the meeting of the American Association for the Study and Control of Rheumatic Diseases, Atlantic City, N. J., June 7, 1937

in its broadest sense, of the general trend of events. We propose to present later, as soon as the bulk of our observations permits, a detailed and final evaluation of the events which have occurred during each year of the first decade of the disease in these 1,000 patients. Until this information is available further statistical considerations can serve no useful purpose, nor can they be considered comparable to the completed ten year study recently reported by Grant¹ on the course of valvular heart disease in 1,000 men.

At this time we are concerned therefore with the incidence and significance of the factors responsible for the fatal outcome in the 306 patients. No patient has been included whose age at the onset of rheumatic fever (or chorea) exceeded 21 years, and the average age for the entire group was 8 years. It is to be emphasized that our observations are relevant only to the first ten years of the disease and embrace essentially the age period from 8 to 18 years, the decade during which rheumatic fever is most prevalent and most damaging to the heart.

TABLE 1—*Causes of Death in 306 Fatal Cases*

		No. of Cases	Percentage
A	Rheumatic fever	250	82
	Rheumatic fever and congestive failure	205	
	Rheumatic fever	24	
	Congestive failure	21	
B	Bacterial endocarditis	18	6
	Acute	4	
	Subacute	14	
C	Other causes related to heart	9	3
	Sudden death	6	
	Cerebral embolus	3	
D	Causes unrelated to heart	16	5
E	Causes unknown	13	4

DATA ON DEATHS

In table 1 we have indicated on the basis of clinical study the causes of death in the 306 fatal cases. The majority of the patients (140) died either at the House of the Good Samaritan or in a general hospital in Boston (85). The clinical notes thereby available render final judgment as to the cause of death reasonably accurate. Postmortem examination was made in 74 instances (24 per cent). In each case in which rheumatic infection had been considered the primary cause of death, the clinical impression was confirmed. Each of the remaining 68 patients for whom we have information relating to the final illness died at home under the care of the family physician. It should be noted that in 16 instances the cause of death was either accidental or irrelevant to our present study. There remain only 13 patients, who are known to be dead but for whom the details of whose final illness are too meager to permit reasonable deductions as to the responsible factors.

1 Grant, R. T. After Histories for Ten Years of a Thousand Men Suffering from Heart Disease, *Heart* 6:275 (June) 1933.

The outstanding cause of death has been rheumatic fever. It was directly responsible for the fatal issue in 250 instances (82 per cent) and was probably an important contributing factor in 19 additional instances.

COURSE OF EVENTS

In table 2 these 250 cases are arranged according to the years which elapsed from the appearance of the first recognizable symptoms of the disease to the time of death. Almost half the patients (47 per cent) succumbed during the first three years, and two thirds (62 per cent) of the fatalities occurred in the first five years. These figures assume increasing significance when it is recalled that the living counterpart of this group of deceased patients represents patients who have been followed for approximately ten years and in many instances well into the second decade of the disease. This feature of the natural course of rheumatic fever, so strikingly displayed by the group who died, is in agreement

TABLE 2—*Duration of Rheumatic Fever from Onset to Death in 250 Cases*

	Duration, Years												
	1	2	3	4	5	6	7	8	9	10	11 to 15	16+	?
Number of cases	57	27	32	18	19	19	16	8	9	8	25	7	5
Percentage	23	11	13	7	8	8	6	3	3	3	10	3	2
Cumulative percentage	23	34	47	54	62	70	76	79	82	85	95	98	100
Age at onset	8.2	8.1	7.5	7.0	8.7	8.1	7.6	7.6	8.1	8.0	8.0	7.5	?

with concurrent observations (as yet unpublished) on the group of living patients. Here the importance of the first five years is also evident as the period beyond which reactivation and hence progression of cardiac disease, is much less likely to occur.

In 94 per cent of our group of patients who died, representing the most unfavorable type of reaction (or disease), evidence of cardiac involvement was present from the onset of rheumatic fever. Furthermore, and perhaps of more fundamental importance, extensive cardiac enlargement occurred early and was noted at the time of the initial attack in all of those who died within the first year of the disease. Significant progression in valvular disease or an increase in the size of the heart with later attacks of rheumatic fever occurred in only 21 of the 153 patients who succumbed during the first five years.

These early years represent clearly a critical period which determines in large measure the future course of the disease. Thereafter the extent of residual cardiac enlargement (and to a lesser degree the rapidity with which it develops) serves as a reliable index of the original susceptibility of the patient's cardiac muscle to previous infection and indicates further its vulnerability to later recurrences of

rheumatic activity Grant has shown in his group of older patients (men) that the degree of functional cardiac limitation is directly related to the size of the heart. With this conception our data are in general agreement, except that in our group of considerably younger patients the dominant role of active rheumatic infection as the determining factor forces other considerations well into the background.

It is to be further noted in table 2 that there was no significant difference between the age at onset of those patients who succumbed to rheumatic fever within the first year of the disease and the age at onset of those who died after a longer period had elapsed. Furthermore, we have been unable to confirm, at least so far as longevity is concerned, the generally accepted impression that the younger the patient at the time of onset of rheumatic fever the less favorable the subsequent course. The data in table 3 reveal no difference in the duration from onset to death in the patients whose disease began during the first five years as compared with the duration in those for whom

TABLE 3—*Duration from Onset of Rheumatic Fever to Death*

	Age at Onset, Years				
	1 to 5	6 to 10	11 to 15	16+	?
Number of patients	61	132	36	16	5
Duration from onset to death, years	4.9	5.0	5.0	8.1	?

the onset dated from the second or third five year period. Our series contains too few patients (16) in whom the disease began after the age of 15 years to warrant the drawing of conclusions, yet the considerably longer duration of life in this small group agrees with our clinical impression and with the observations of others² that the age of puberty represents a second, and in this instance favorable, landmark in the natural course of the disease.

CLINICAL OBSERVATIONS

In certain important respects the clinical picture of severe, and in this group fatal, rheumatic fever differs profoundly from that represented by the earlier manifestations of the disease. It is frequently confused with the clinical picture of primary disease of the lungs (pneumonia) of the kidneys (acute nephritis) or of uncomplicated heart disease.

The fatal illness, the beginning of which was often poorly defined, we have called for convenience terminal. In the majority it represented an exacerbation of long-standing and clinically recognizable

² Wilson, M. G. The Natural History of Rheumatic Fever in the First Three Decades, *J. Pediat.* **10**: 456 (April) 1937.

rheumatic fever. The duration of this so-called terminal illness usually extended over a period of months before the patient eventually succumbed to an exacerbation of toxic symptoms with increasing signs of heart failure. Less often the initial attack of rheumatic fever progressed to a fatal termination without a recognizable interval of significant improvement. In 4 of the patients showing the most rapidly fatal involvement the duration from the first appearance of symptoms of the disease to the time of death was three months, whereas in 25 additional patients death ensued within six months of the onset. In a few instances a fulminant recrudescence of apparently quiescent infection ended fatally in as short a period as ten days (chart).

TABLE 4—*Clinical Manifestations of Rheumatic Fever During Fatal Illness in 250 Cases*

		No. of Cases	Percentage
I	Major manifestations (so called)		
1	Arthritis	0	
2	Chorea	2	
3	Nodules (see text)	49	60
4	Carditis	250	100
	A. Struc		
	a	250	100
	b	250	100
	c Pericarditis (friction rub)	17*	35
	B. Functional manifestations		
	a Tachycardia	135*	100
	b Congestive failure	229	90
	c Delayed auriculoventricular conduction (electrocardiographic study in 87 cases)	77	30
	d Auricular fibrillation	15	18
II	Pulmonary signs		
1	Consolidation or pleurisy (friction rub)	38*	25
III	Hepatic signs		
1	Enlargement of liver	135*	100
2	Jaundice	1	

* On the basis of 135 patients who died of rheumatic fever at the House of the Good Samaritan.

It is beyond the scope of this report to review the more generally recognized manifestations of rheumatic fever other than to indicate certain features of the severe form which have been especially prominent in this group. The clinical picture prior to the fatal recrudescence is one of poor health, pallor, loss of weight, variable discomfort in the joints, muscles, chest and abdomen and often a low grade febrile reaction, with cyclic exacerbations. Superimposed on this ill defined syndrome of poor health in childhood or adolescence is a fairly characteristic group of symptoms and signs. Clinical observation and post-mortem study have shown that they represent the manifestations of severe rheumatic fever. In table 4 these clinical features are arranged under three headings, as follows:

1 *Major Manifestations*—In the first division we have indicated the incidence during the fatal illness of the four so-called major mani-

festations of rheumatic fever. This designation not only possesses some merit from established usage but is helpful in contrasting the symptoms and signs of severe rheumatic fever with the more generally recognized clinical picture of the disease. It is evident that important differences exist.

Arthritis. Arthritis, manifested by acutely painful, tender or swollen joints, was not present in any case during the course of the terminal illness. A history of arthritis, however, either at the onset of the original infection or with later recrudescences was common. Although arthritis

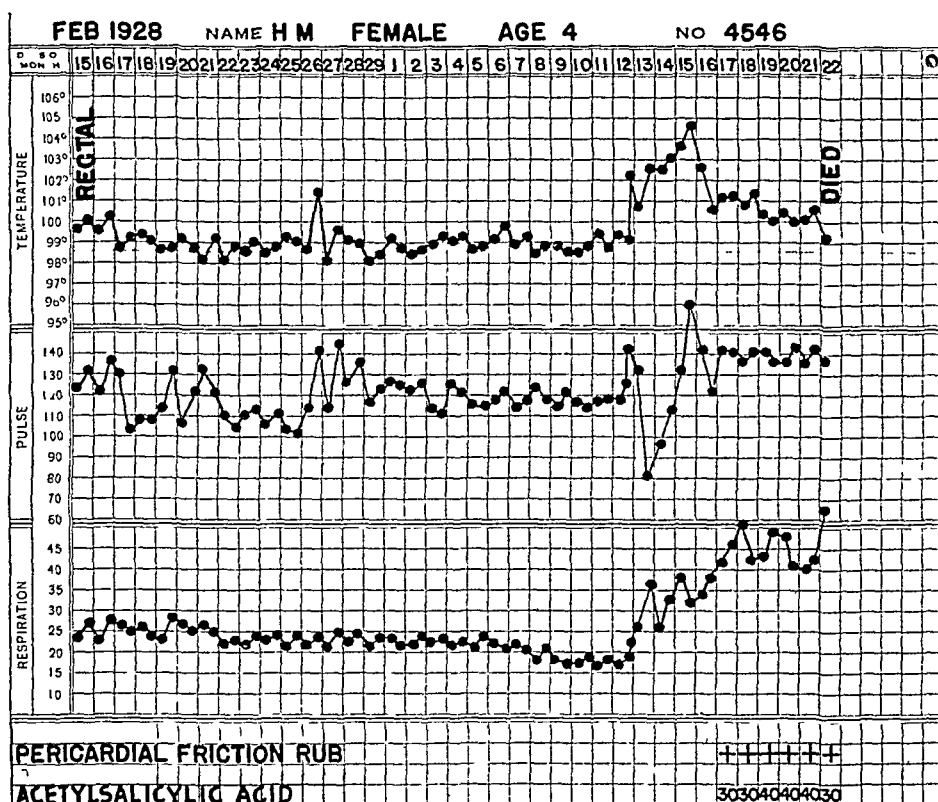


Chart showing a fulminant and fatal recrudescence of clinically quiescent rheumatic fever two weeks after an unexplained and transient elevation of temperature (J Clin Investigation **14** 633 [Sept] 1935)

was absent, variable arthralgia causing sufficient discomfort to require salicylate therapy was observed in approximately half the group. It was never a prominent feature. Far more troublesome were abdominal and precordial pain, the latter occasionally requiring opiates for relief. The striking absence of arthritis and the relative mildness of articular manifestations in this group of patients with the most severe type of rheumatic fever need special emphasis. It is clear that if one fails to dissociate the two, the true nature of the severe form of the disease will be frequently overlooked.

Chorea Chorea was rarely encountered. In only 2 patients was it present during the terminal illness, in both instances being manifested by a mild form of incoordination. In 53 (21 per cent) of the total group of 250 patients who died of rheumatic fever, chorea as a manifestation of rheumatic activity had been present during past illnesses, as compared with an incidence of 57 per cent for those still living. This further supports our previously expressed opinion that chorea is usually associated with a relatively mild form of rheumatic fever.³ Chorea insaniens was not observed in the group of patients who died and has not been observed in those still living.

Subcutaneous Nodules Subcutaneous nodules were present in 49 of the 83 patients (60 per cent) who have died at the House of the Good Samaritan since 1930. These structures are often found only after diligent search, being easily overlooked in a careful but otherwise routine examination. We have therefore based the incidence on the post-mortem data for patients personally observed by us during the past six years. Rheumatic nodules appear to be of no prognostic significance other than with respect to their characteristic association with a severe and protracted form of the disease.

Carditis Carditis was the only one of the four major manifestations present in every patient. Extensive and active involvement of the heart was manifested clinically by marked enlargement (dilatation), tachycardia, characteristic murmurs and ultimately failure of the congestive type. In a few instances of unusually fulminant rheumatic infection death ensued before the appearance of general venous engorgement. However, carditis was recognized clinically in 90 per cent of those who died of rheumatic fever.

The significance of the occurrence of congestive heart failure in patients with rheumatic heart disease during the first two decades of life, previously discussed by others,⁴ is worthy of further emphasis. We have reason to believe it is not generally appreciated that heart failure in this age group is not primarily an expression of mechanical strain, but represents activity of the essential rheumatic process in the heart. The course in our fatal cases, supported by postmortem study as well as parallel observations on our group of living patients, is in agreement with this conception. Although in cases of otherwise obscure involvement careful search usually reveals evidence of rheumatic activity, occasionally heart failure remains the only demonstrable evidence. The presence of nodules, otherwise often overlooked, has been particularly

3 Jones, T. D., and Bland, E. F. Clinical Significance of Chorea as a Manifestation of Rheumatic Fever, *J. A. M. A.* **105**: 571 (Aug. 24) 1935.

4 Rothschild, M. A., Kugel, M. A., and Gross, L. Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During the Various Age Periods, *Am. Heart J.* **9**: 586 (June) 1934.

helpful in disclosing clinically the relation between active rheumatic fever and heart failure—a relation to which postmortem study in this series has as yet revealed no exceptions. Therefore in 21 instances in which the clinical notes were otherwise inadequate we have considered the presence of congestive failure as evidence per se of active rheumatic fever.

Acute fibrinous pericarditis recognized clinically by a pericardial friction rub was noted during the final illness in 35 per cent of the 135 patients who died of rheumatic fever at the House of the Good Samaritan. Of those studied post mortem 55 per cent showed evidence of acute pericardial inflammation whereas 80 per cent showed evidence of either acute or chronic pericardial involvement. Excessive amounts of pericardial fluid, beyond 200 cc. were rarely encountered. In 1 instance 800 cc. was removed by paracentesis and in a second instance 1 200 cc. was removed post mortem. In the latter instance pericardial paracentesis in the fifth left interspace just inside the left border of cardiac dullness had yielded arterial blood (left ventricle) and no fluid. It is of further interest that in spite of the high incidence of pericardial involvement with rheumatic fever no instance of Pick's syndrome has yet been encountered.

Electrocardiograms taken at frequent intervals for the patients who have died in the House of the Good Samaritan since 1928 proved to be of no value in predicting the fatal outcome. In 40 per cent there was a delay in the auriculoventricular conduction time beyond the accepted normal of one-fifth second. In only 2 instances was the delay of sufficient extent to cause "dropped beats." It happened that these 2 patients were receiving moderate amounts of digitalis which may have been in part responsible for the higher degree of block. No instance of complete auriculoventricular dissociation or of an intraventricular conduction defect was encountered. An abrupt and striking slowing of the pulse rate from a level of from 110 to 130 to a level of from 60 to 70 per minute occurred for a few hours before death in 6 patients. In 1 instance an electrocardiogram was obtained during this phenomenon and showed sinus bradycardia but no defect in conduction. The explanation for this occasionally observed terminal slowing of the pulse remains obscure.

Auricular fibrillation was present in 18 per cent of the patients, in spite of the youthfulness of the majority of them. The youngest patient in whom we have seen this arrhythmia was 7 years old, this disorder being the terminal event for two days prior to death. It may have been significant that this patient was receiving full doses of digitalis at the time. The youngest patient with established fibrillation was 9 years of age and the arrhythmia persisted until death occurred two years later. In 4 additional cases auricular fibrillation ensued at the age of 11 years.

It is of considerable significance that in 36 (80 per cent) of a total of 45 patients who had auricular fibrillation a recrudescence of rheumatic fever was clearly the precipitating event. Paroxysmal tachycardia (presumably of auricular origin) occurred in 5 patients during severe rheumatic fever. Death occurred abruptly during the course of severe infection in 17 of the children who died at the House of the Good Samaritan. It suggests as a terminal event the occasional occurrence of either ventricular fibrillation or standstill of the heart.

2 *Pulmonary Signs*—Evidence of involvement of the lung other than the simple congestion of heart failure or an associated pleural effusion was observed in 28 per cent of the patients under observation in the hospital during their final illness. Areas of consolidation, variable in size and distribution but usually bilateral, were encountered during severe exacerbations, especially in the cases of fulminant involvement. An associated pleural friction rub was common with underlying consolidation, less often a friction rub alone constituted the only clinical sign of pulmonary and pleural involvement. Post mortem these areas of consolidation represented gross hemorrhage in the pulmonary tissue which has been discussed by others and designated rheumatic pneumonia. The physical signs associated with these lesions in a number of instances prior to study in the hospital were incorrectly attributed to primary disease of the lungs (pneumonia). It is to be emphasized that in our experience we have not encountered this consolidation as an isolated phenomenon but only as a complication in patients otherwise ill with a severe type of rheumatic fever.

3 *Hepatic Signs*—In the present series striking changes were constantly observed in the liver both clinically and pathologically. In previous reports the hepatic signs have received relatively little attention. Enlargement (and tenderness) of the liver, both in the absence of and out of proportion to general venous engorgement, has been an outstanding feature in the fatal cases. Postmortem observation not only confirms the constancy of this finding but reveals characteristic changes. Grossly the appearance is that of an enlarged congested liver presenting on section an unusually mottled "nutmeg" appearance. In cases of extreme involvement extensive areas of hemorrhage are present and occasionally deposits of fibrin superficially. Microscopic examination reveals widespread destruction of hepatic cells in the central portion of the lobules out of proportion to and apparently independent of the degree of associated congestion. The pattern in cases of severe involvement resembles that observed in certain types of severe toxemia. In spite of the extensive damage, clinical jaundice was rarely encountered (4 instances). So impressed have we been by the alterations observed post mortem that a detailed investigation of their significance is now in progress.

OTHER CONSIDERATIONS

From the total group of 306 patients who have died there remain 56 (18 per cent) in whom factors other than rheumatic fever were primarily responsible for the fatal termination

Secondary bacterial infection of cardiac valves previously scarred by rheumatic fever accounted for 18 deaths (6 per cent). In 4 of these 18 patients acute bacterial endocarditis was responsible for death. The youngest patient was 3 years of age, and a pneumococcus was the causative organism. In the remaining 14 cases the clinical course was that of subacute bacterial endocarditis. *Streptococcus viridans* was the responsible agent in each instance. The youngest patient who died of subacute bacterial endocarditis was 6 years of age, death occurring three years after the onset of rheumatic fever. It seems to us that 6 per cent is a discouragingly high figure in view of the fact that we are dealing here with a group of young patients during the first decade after rheumatic fever and an age group in which bacterial endocarditis (especially the subacute type) is generally considered an infrequent complication.

There remain a few additional instances in which the cause of death was apparently related to the heart. Sudden death occurred in 6 patients with known rheumatic heart disease. We have observed sudden death in older apparently well patients in whom postmortem study revealed active rheumatic myocarditis as the only reasonable explanation⁵. It happened that autopsies were not performed on this group of 6 patients. In 3 of the remaining patients cerebral embolism, unassociated with known rheumatic activity or with bacterial endocarditis, resulted in death. In the remaining 29 patients the cause of death was either clearly unrelated to the heart or, as in 13 instances, entirely unknown.

SUMMARY AND CONCLUSIONS

Since 1921 (sixteen years) approximately 1,500 children and adolescents under the age of 21 years have received hospital care at the House of the Good Samaritan for rheumatic fever and chorea. The subsequent course and present status of this large group are known. We have presented in this report data relevant to the 306 patients who have died. Postmortem examination was made in 74 instances (24 per cent). From a consideration of this group of patients who have died the following conclusions may be cited:

1. Rheumatic fever has been the outstanding cause of death and was directly responsible for the fatal issue in 250 instances (82 per cent).

⁵ Rheumatic Myocarditis, Cabot Case 22041, *New England J. Med.* **214** 154 (Jan. 23) 1936.

2 The early years after the onset of the disease have proved to be a critical period. In approximately half (47 per cent) of the fatal cases death occurred during the first three years and in two-thirds (62 per cent) during the initial five years.

3 Thereafter the extent of residual cardiac enlargement (dilatation) and, to a lesser degree, the rapidity with which it developed have served as the most reliable criteria of the severity of the preceding infection as well as an index of the future susceptibility of the individual patient to subsequent fatal rheumatic fever.

4 The age of the patient at the time of onset of rheumatic fever (or chorea) during the first fifteen years of life has been of no significance so far as subsequent longevity is concerned.

5 The manifestations of fatal rheumatic fever have been stressed and contrasted with the generally accepted clinical picture of the disease.

ATYPICAL FACIAL NEURALGIA

AN ANALYSIS OF TWO HUNDRED CASES

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AND

H MARLIN BEERMAN, M D

LOS ANGELES

The occurrence of continuous and obscure pains about the face and head for which the usual methods of relief, both medical and surgical, have as a rule failed has been the subject of considerable investigation since 1920. The patients whose records are here analyzed have run the gantlet of numerous physicians, both local and foreign, 1 patient (who is a physician) having visited 126 physicians in America and on the Continent. Useless and meddlesome surgical procedures have been performed not only on the trigeminal tract but on the nasal sinuses, the abdomen and the pelvis, and there has been wholesale extraction of teeth as well. Peculiarly enough, not only have these operations failed to accomplish their purpose, but in practically all cases the pain has been much worse thereafter.

Though many of these patients complain bitterly of pain during the examination, their facies rarely indicate such severity. This is in contradistinction to patients with trigeminal neuralgia, who during an attack show every indication of the excruciating nature of the pain.

From 1908 to 1916 Sluder¹ observed that the bony partition separating the accessory nasal sinuses from the sphenomaxillary fossa may be extremely thin or even defective. He said he believed that inflammation within these cells may cause involvement of the sphenopalatine ganglion, with the resulting development of a neuralgic syndrome, which he described as follows:

The neuralgic picture is pain in the root of the nose and in and about the eye, in the upper jaw and teeth (sometimes lower jaw and teeth) extending backward under the zygoma to the ear, frequently making earache and pain in the mastoid but severest often at a point 6 cm back of the mastoid, extending thence to the occiput, neck, shoulder-blade, shoulder, breast, and when severe, to the arm, forearm, hand and fingers, with sometimes a sense of sore throat on that side. Rarer additions to this picture are itching of the skin of the upper extremity, taste disturbances (parageusia), a sense of stiffness and muscle weakness in the upper extremity and fortification scotomata. Mild cases are described as a sense

1 Sluder, G. Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1918.

of tension in the face and stiffness or rheumatism in the shoulders. It may appear as a constant pain with exacerbations, or it may stop and reappear cyclically as a migraine, or it may stop and reappear with stabbing sharpness as a tic.

In 1920 Cushing² reported the case of a woman 35 years of age, who first came under his observation in 1906 because of facial pain. After numerous injections of alcohol, peripheral neurectomy and excision of the trigeminal root, she still complained of pain in spite of the existence of anesthesia. A diagnosis of sphenopalatine neuralgia was made, and twice injection of alcohol into the sphenopalatine ganglion was attempted without affording relief. Finally the sphenopalatine ganglion was surgically removed, still without relief. In January 1920, thirteen years later, the patient still had the original pain. Cushing has observed 6 or 8 similar cases, and this experience has led him to beware of patients with this type of pain.

In 1923 Davis³ reported on a patient with continuous pain in the face, right enophthalmos, with drooping of the upper eyelid, a slightly smaller pupil on the right and increased lacrimation on the right. This patient was not relieved by injections of alcohol or of cocaine into the sphenopalatine ganglion.

In 1923 Frazier and Russell⁴ called attention to the existence of a miscellaneous group of these neuralgias to which, for want of better understanding as regards origin and treatment and for want of better terminology, the name atypical neuralgia was applied. After analyzing 60 cases they enumerated some diagnostic points which enable one to differentiate these neuralgias from true trigeminal neuralgia, thus avoiding section of the sensory root. At that time they emphasized the constant character of the pain, stating definitely that it was not intermittent but paroxysmal, though varying in its intensity.

Reid and Eckstein,⁵ in 1924, called attention to cases of neuralgia of the face in which relief was not obtained by excision of the trigeminal nerve. They quoted Heuer, who had the opportunity of examining a patient who had been operated on eight years before and was not completely relieved by division of the sensory root of the fifth nerve. They found that pressure on the superior cervical ganglion produced

2 Cushing, Harvey. The Varieties of Facial Neuralgia, *Am J M Sc* **160** 157 (Aug.) 1920.

3 Davis, Loyal E. Lesions of the Paratrigeminal Area, *J A M A* **80** 380 (Feb. 10) 1923.

4 Frazier, C. H., and Russell, Ethel C. Neuralgia of the Face. An Analysis of Seven Hundred and Fifty-Four Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, *Arch Neurol & Psychiat* **11** 557 (May) 1924.

5 Reid, Mont R., and Eckstein, Gustav. Sensory Disturbances Following Sympathectomy for Angina Pectoris, *J A M A* **83** 114 (July 12) 1924.

pain in all three branches of the fifth nerve, though the face was totally anesthetic. Three years later Fay⁶ again called attention to the sign and applied the word carotidynia.

Parker,⁷ in 1924, described several cases of unusual facial pain in the area of the fifth nerve, resulting from various etiologic factors. He further deplored the use of the word atypical, which was in line with the opinion of Frazier and Russell.

In 1928 Glaser⁸ reviewed the cases from Frazier's clinic and found 245 examples of the atypical variety. From the 245 he segregated 143 with similarity of symptoms, namely, the lack of response to therapy and the absence of any etiologic factor. Because of inability to supply a better name than that first suggested by Frazier, this particular group was defined as representing atypical neuralgia. From this study a clear-cut syndrome was drawn up. No method of treatment was suggested, as all attempts directed toward relief had failed, and attention was called to the importance of the recognition of these cases.

In this original analysis of 143 cases, constancy of pain also was dominant. In none of the cases was there evidence of short attacks of pain lasting for from several hours to several days. In cases in which an intermission of several years occurred an oppressive sensation persisted. None of these attacks could be considered intermittent or paroxysmal. Those of this nature were entirely eliminated from the analysis and belonged among the remaining 102 cases eliminated from this series.

Reports concerned with patients suffering from obscure facial pains have appeared in the literature from time to time (Foerster,⁹ Halphen, Monbrun and Tournay,¹⁰ Peet,¹¹ Grant,¹² Flothow,¹³ White,¹⁴

6 Fay, Temple. Atypical Neuralgia, *Arch Neurol & Psychiat* **18** 309 (Aug.) 1927, Atypical Facial Neuralgia, A Syndrome of Vascular Pain, *Ann Otol, Rhin & Laryng* **41** 1030 (Dec.) 1932.

7 Parker, Harry L. Unusual Forms of Pain in the Area of the Fifth Nerve, *J A M A* **83** 1672 (Nov. 22) 1924.

8 Glaser, Mark A. Atypical Neuralgia, So-Called. A Critical Analysis of One Hundred and Forty-Three Cases, *Arch Neurol & Psychiat* **20** 537 (Sept.) 1928.

9 Foerster, O. *Deutsche Ztschr f Nervenhe* **106** 109 (Dec.) 1928.

10 Halphen, Monbrun and Tournay. Les cephelees en oto-neuro-ophtalmologie, *Physiologie pathologique et traitement*, *Rev d'oto-neuro-opht* **7** 161 (March) 1929.

11 Peet, Max. Minor. The Rôle of the Sympathetic Nervous System in Painful Diseases of the Face, *Arch Neurol & Psychiat* **22** 313 (Aug.) 1929.

12 Grant, Francis. Personal communication to the authors, Jan. 20, 1930.

13 Flothow, P. G. Relief of Pain from a Neurological Viewpoint, *Northwest Med* **29** 69 (Feb.) 1930.

14 White, James C. Progress in the Surgery of the Sympathetic Nervous System in 1932, *New England J Med* **209** 843 (Oct. 26) 1933.

Mixter and White,¹⁵ Reichert,¹⁶ Davis and Pollock,¹⁷ Abbott,¹⁸ Wilson,¹⁹ Fincher,²⁰ Turner,²¹ Braeucker,²² Marks,²³ Bryan,²⁴ Hyslop,²⁵ Brickner and Riley,²⁶ Merwarth²⁷ and Cobb and Mixter²⁸)

The present paper deals with 200 cases in which there was constant pain (143 of these cases have been previously reported) and which have been analyzed in order to show some of the characteristics. A further classification of obscure facial pains, as well as the etiology and treatment in some cases, will be the subject of another communication.

Numerous operations have been performed for the relief of atypical facial neuralgia but none of them has been successful in this particular group. In approximately half the cases included in table 1 the patient was unable to relate the onset of pain to any particular cause, though in table 2 there may be noted numerous coincidental events from which the patient thought the pain might have originated. According to table 3 the onset was most common in the third decade of life, and in the majority of cases the pain developed in early life. Females greatly predominated over males, as shown in table 4, while table 5 shows that the pain occurred on the right, on the left and bilaterally almost equally. The distribution of the pain followed, in general, a circular area within the facial vascular supply. The pain was felt in the chin, along the nose, around the eye over the brow, to the vertex or temporal region, in front of, in or

15 Mixter, J. J., and White, J. C. Pain Pathways in the Sympathetic Nervous System, *Arch Neurol & Psychiat* **25** 986 (May) 1931

16 Reichert, F. L. Neuralgias of Head and Face, *Am J M Sc* **187** 362 (March) 1934

17 Davis, Loyal, and Pollock, Lewis J. The Role of the Sympathetic Nervous System in the Production of Pain in the Head, *Arch Neurol & Psychiat* **27** 282 (Feb.) 1932

18 Abbott, W. D. Diagnostic and Therapeutic Injections of the Sympathetic Nervous System, *Nebraska M J* **17** 293, 1932

19 Wilson, David C. Atypical Facial Neuralgia, *J A M A* **99** 381 (Sept 3) 1932

20 Fincher, Edgar, in discussion on Wilson¹⁹

21 Turner, Carroll C., in discussion on Wilson¹⁹

22 Braeucker, W. Die Fortschritte und die Zukunft der Sympathicuschirurgie. *Nervenarzt* **6** 449, 1933, Ueber typische und atypische Formen von Gesichtsnuralgien, *Zentralbl f Chir* **60** 2454, 1933

23 Marks, S. B. Sympathetic Nervous System as a Causative Factor in Atypical Neuralgia, *Kentucky M J* **32** 393 (Aug.) 1934

24 Bryan, A. W. Neuralgias of the Head and Neck, *Wisconsin M J* **34** 320 (May) 1935

25 Hyslop, G. H. Face Pain, *New York State J Med* **36** 91 (Jan 15) 1936

26 Brickner, Richard M., and Riley, Henry Alsop. Autonomic Facio-Cephalalgia, *Bull Neurol Inst New York* **4** 422 (Dec.) 1935

27 Merwarth, Harold R., and Freimann, I. Practical Neurologic Therapy. *M Times & Long Island M J* **64**:2 (Jan.) 1936

28 Cobb, S., and Mixter, J. Lingual Spasm. *Ann Surg* **101** 49 (Jan.) 1935

TABLE 1—*Number of Operations of Various Types*

Injection of alcohol in branches of trigeminal nerve	70
Injection of cocaine into sphenopalatine ganglion	66
Extraction of teeth	74
Operation on sinuses	60
Avulsion of supra orbital and infra orbital nerves	24
Nasal operation	21
Cervical sympathectomy	12
Stripping of periarterial carotid plexus	10
Subtotal section of sensory root of trigeminal nerve	12
Mastoidectomy	8
Pelvic operation	8
Paravertebral block	3
Appendectomy	2
Tonsillectomy	2
Operation on brain	1
Removal of lipoma of left eye	1
Excision of artery	1

TABLE 2—*Coincidental Events*

Extraction of teeth	38
Accidents	
War wounds	4
Automobile accident	9
Railroad accident	2
Blow on head	1
Diseases	
Influenza	7
Cold	4
Gastro intestinal disorder	2
Operation	13
Worries	9
Pregnancy	1
Nervous breakdown	3
Facial tic	1
Cocaine addiction	1
Unknown	105

TABLE 3—*Age at Onset*

Age	Number of Cases
0-10	19
10-20	39
20-30	56
30-40	38
40-50	22
50-60	11
Unknown	15

TABLE 4—*Incidence According to Sex*

Sex	Number of Cases
Male	48
Female	152

TABLE 5—*Side Involved*

	Number of Cases
Left	66
Right	58
Both	76

or a ball of fire or electricity in the eye. Some patients described it as twitching, severe, jumpy, crawling, unbearable, wearing, pounding, surging, crushing, vibrating, excruciating or grabbing.

The pain was chronic, persistent and continuous, and associated with it were attacks of greater or less severity, which would come on either acutely or insidiously. If an attack of pain had an insidious onset, it would gradually increase in intensity over a period of from several hours to several days. Then the pain would be at its height over a period of from several hours to several days. During the period of most severe pain associated sympathetic phenomena were present in some cases and the patient would necessarily be confined to bed. The attack might then

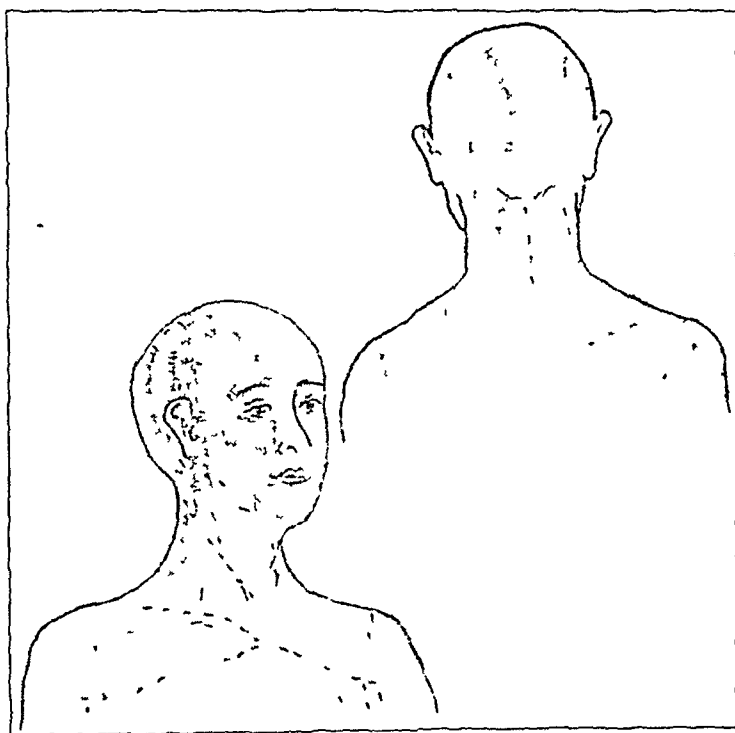
TABLE 7—*Type of Pain*

	Number of Cases
Dull aching	88
Throbbing	58
Burning	53
Shooting	50
Sharp	42
Sense of pressure	39
Drawing	30
Needle like	26
Boring	24
Toothache	22
Pulling	21
Soreness	18
Gnawing	17
Bursting	14
Tearing	14
Electricity	14
Hot iron	12
Tingling	11
Smarting	11
Nagging	11
Knifelike	9
Beating	9
Stinging	9
Prickling	8
Bugs creeping	8
Itching	8
Gripping	7
Lightning	4

either suddenly subside or gradually disappear. After that there was the chronic phase of the disease. These attacks might occur at intervals of several days to even months, but during the interim between attacks the patient was never free from pain. If a remission did occur, as it did in a few cases, the picture of the neuralgia did not give the impression of being paroxysmal or intermittent. It is the constancy of the pain that makes up this syndrome. In no case in this particular group was relief obtained by any therapeutic measure, though table 8 indicates some of the methods whereby a certain amount of ease was found. The local factors that aggravated the pain consisted of eating, contact, brushing the teeth, blowing the nose, sneezing, swallowing and shaving and were present in 35 cases, whereas in the remaining 165 cases general factors were responsible for the onset. In all the cases in which local factors

were responsible for aggravating the pain, general factors also brought on the attack. Sympathetic phenomena were present in 90 cases, whereas in the remaining 110 cases there was no sympathetic involvement.

This pain must be mainly differentiated from that of trigeminal neuralgia. The incidence of tic douloureux is equal in the two sexes, whereas in the cases of atypical neuralgia females predominate. Tic douloureux is bilateral in only 2 per cent, whereas atypical neuralgia is bilateral in one third of the cases. Tic douloureux usually occurs in persons over 35 years of age, whereas atypical neuralgia occurs more frequently in younger persons. Tic douloureux always follows the



The distribution of the pain in atypical facial neuralgia

distribution of the trigeminal nerve, whereas atypical neuralgia follows the distribution of no single cranial nerve. The pain in tic douloureux is superficial, whereas that of atypical neuralgia is deep. When the trigeminal nerve is affected, there are intervals of freedom from pain, whereas in cases of atypical neuralgia pain of some type is always present. Both of these diseases may be marked by attacks of pain, but the attack of trigeminal neuralgia is short and terrifically painful, while the attack of atypical neuralgia is long, with pain of less intensity. The type of pain in trigeminal neuralgia is lancinating sharp and knifelike, whereas that of atypical neuralgia is aching, burning and nagging, being extremely difficult to describe. The pain of trigeminal neuralgia is brought on by the slightest local contact, while that of atypical neuralgia

is brought on by more generalized factors, such as cold, fatigue or excitement. Trigger zones occur in trigeminal neuralgia, while tenderness of the cervical sympathetic ganglion or the cervical artery is present

TABLE 8—*Factors Which Eased the Pain*

	Number of Cases
Acetylsalicylic acid	31
Heat	24
Morphine	23
Nothing	18
Pressure	13
Lying down	11
Cold	9
Codeine	8
Massage	6
Dark room	4
Smoking	3
Chewing (paraffin in 2 cases)	3
Epinephrine hydrochloride (spray)	2
Hot weather	2
Pressure on jugular vein	2
Nonuse of eyes	1
Chloral hydrate	1

TABLE 9—*Factors Aggravating the Pain*

	Number of Cases
Local	
Cold	68
Draft	34
Heat	32
Eating	22
Light	14
Contact	15
Brushing teeth	12
Vibrating	11
Reading	15
Wind	8
Blowing nose	8
Sneezing	8
Swallowing	6
Shaving	2
General	
Fatigue	63
Excitement	48
Menses	36
Worry	34
Talking	27
Winter	15
Exertion	17
Night	16
Lying down	17
Stooping	13
Morning	11
Noise	18
Damp	13
Motion	3
Cough	7
Arguments	1
Washing face	1
Constipation	1
Nothing	14

in atypical neuralgia. Tic douloureux is entirely without associated sympathetic phenomena, but in approximately 50 per cent of the cases of atypical neuralgia there are sympathetic phenomena.

As there are other cranial nerves which have a sensory supply to the face, it may occasionally be found that a disorder of these nerves is confused with atypical facial neuralgia. These neuralgias are paroxysmal, with acute lancinating pain referred to the distribution of the nerve involved. Foremost among this group is glossopharyngeal neuralgia,

TABLE 10—*Sympathetic Phenomena*

	Number of Cases
Ocular disturbance	
Lacrimation	52
Edema	46
Corneal injection	26
Unequal pupils	20
Blurred vision	6
Photophobia	4
Enophthalmos	2
Nausea	39
Vomiting	34
Flushing of face	28
Nasal discharge	21
Perspiration	14
Salivation	11
Puffy face	13
Feeling of warmth	2
ringing in ears	2
Soreness over temporal artery	1
Chills	2
Aural discharge	3

TABLE 11—*Differentiation of Tic Douloureux and Atypical Neuralgia*

	Tic Douloureux	Atypical Neuralgia
Sex incidence	Equal	Predominance of females
Bilateral pain	In 2% (approximate)	In 33% (approximate)
Age	35 years and over	35 years and under
Distribution	Trigeminal nerve	No single cranial nerve
Attacks	Momentary, very severe	Long, less severe
Pain	Intervals of freedom	Continuous
	Superficial	Deep
	Lancinating, sharp knifelike	Aching, boring, throbbing, ex- tremely difficult to describe
Onset following	Slightest stimulation of skin or mucous membrane	Cold, fatigue, excitement
Trigger zones	Trigger zones along tri- geminal nerve (frequently)	Tenderness on pressure in area of carotid and cervical sympathetic ganglions (frequently)
Sympathetic phenomena	None	In 50%
Narcotic addiction	None	Frequent

in which the pain is paroxysmal, sharp, shooting and lancinating, usually beginning in the throat or tonsillary region or back of the tongue, then radiating in front of the ear, down the throat into the jaw and occasionally into the neck. Occasionally these patients complain of a "hacking" cough, sometimes the tic seems to be relieved by pain in the ear and occasionally a feeling of dryness of the mouth and salivation accompanies the syndrome. A trigger zone at times may be found at the

base of the tongue or tonsillar region, and an injection of cocaine will temporarily relieve the attack. These attacks are always brought on by an effort on the part of the patient, such as talking, eating or swallowing. Surgical section of the glossopharyngeal nerve always relieves the pain (Weisenburg,²⁹ Harris,³⁰ Doyle,³¹ Sicard and Robineau,³² Reichert,³³ Adson,³⁴ Dandy³⁵ and Stookey³⁶).

In 1927 Fay³⁷ expressed the opinion that the sensory fibers of pain distribution to the pharynx and to the region of the ear, in the zone of so-called glossopharyngeal neuralgia, do not correspond to a function of the ninth nerve and its intracranial representation. He said he considered this syndrome as a manifestation of the tenth nerve in the sensory portion and suggested the name vagal auricular pharyngeal neuralgia. No work has been carried out to corroborate Fay's opinion, and in view of the numerous cases of glossopharyngeal neuralgia in which relief has followed section of the ninth nerve, this idea has not gained recognition.

Neuralgia of the superior laryngeal nerve has been described by Avellis,³⁸ Hutter,³⁹ Bailey,⁴⁰ Harris³⁰ and Echols and Maxwell.⁴¹ It is

29 Weisenburg, T. H. Cerebellopontile Tumor Diagnosed for Six Years as Tic Douloureux. The Symptoms of Irritation of the Ninth and Twelfth Cranial Nerves, *J. A. M. A.* **54** 1600 (May 14) 1910.

30 Harris, Wilfred. Neuritis and Neuralgia, London, Oxford University Press, 1926.

31 Doyle, J. B. A Study of Four Cases of Glossopharyngeal Neuralgia, *Arch. Neurol. & Psychiat.* **9** 34 (Jan.) 1923.

32 Sicard, R., and Robineau. Algie velopharyngee essentielle, traitement chirurgical, *Rev. neurol.* **27** 256, 1920.

33 Reichert, Frederick Leet. Glossopharyngeal Neuralgia, *West. J. Surg.* **39** 347 (May) 1931.

34 Adson, A. W. The Surgical Treatment of Glossopharyngeal Neuralgia, *Arch. Neurol. & Psychiat.* **12** 497 (Nov.) 1924.

35 Dandy, W. E. Glossopharyngeal Neuralgia (Tic Douloureux). Its Diagnosis and Treatment, *Arch. Surg.* **15** 198 (Aug.) 1927.

36 Stookey, B. Glossopharyngeal Neuralgia. Surgical Treatment, with Remarks on the Distribution of the Glossopharyngeal Nerve, *Arch. Neurol. & Psychiat.* **20** 702 (Oct.) 1928.

37 Fay, Temple. Intracranial Division of Glossopharyngeal Nerve Combined with Cervical Rhizotomy for Pain in Inoperable Carcinoma of the Throat, *Ann. Surg.* **84** 456, 1926.

38 Avellis, G. Typische Form von Kehlkopfneuralgie, *München med. Wchnschr.* **47** 1592 (Nov. 13) 1900.

39 Hutter, F. Ueber Neuralgien des Nervus laryngeus superior, *Monatschr. f. Ohrenh.* **63** 402 (April) 1929.

40 Bailey, Percival. Neuralgias of Cranial Nerves, *S. Clin. North America* **11** 61 (Feb.) 1931.

41 Echols, Dean H., and Maxwell, James H. Superior Laryngeal Neuralgia Relieved by Operation, *J. A. M. A.* **103** 2027 (Dec. 29) 1934.

characterized by paroxysms of unilateral pain, which radiates from the side of the thyroid cartilage to the angle of the jaw and occasionally to the ear. There is a trigger zone at the plica of the nerve in the pyriform sinus. Swallowing will bring on an attack. There is a sensitive point superficially situated, above and lateral to the thyroid cartilage, where the nerve pierces the hyothyroid membrane.

The sensory innervation of the auricle and surrounding skin is complex. The trigeminal, the facial, the vagus and pneumogastric (it is almost impossible anatomically to separate the pneumogastric sharply from the vagus nerve), the glossopharyngeal and the greater auricular nerve, which arises from the second and third cervical nerves, supply this area. As these areas overlap considerably, it is extremely difficult to determine the exact nerve responsible for pain. There is a group of neuralgias of the acute lancinating variety which has been variously described in the literature under different names. Hunt⁴² said he believed that the pain is due to involvement of the facial nerve. Taylor and Clark⁴³ operated on a patient and demonstrated that the pain was in the pars intermedia of Wrisberg. Reichert⁴⁴ operated on another patient, demonstrating the glossopharyngeal nerve as the responsible factor. Hall⁴⁵ stated that he was under the impression that the greater auricular nerve caused the pain in his particular patient. Suffice it to say that acute neuralgia is extremely rare but must be considered in conjunction with vidian and sphenopalatine neuralgias in their differentiation from the more chronic type of so-called atypical neuralgia.

CONCLUSIONS

The term atypical neuralgia is not satisfactory but has been used by Frazier, Russell and Glaser to describe a peculiar deep-seated, aching pain that is constant, not paroxysmal or intermittent, but marked by attacks of greater or less severity, occurring at varying intervals. Remissions are rare. Associated with this pain are sympathetic phenomena in 50 per cent of the cases. The pain does not follow the distribution of any of the cranial nerves and involves the scalp as well as the face.

42 Hunt, J. Ramsay. Otagia Considered as an Affection of the Sensory System of the Seventh Cranial Nerve, *Arch Otol* **36** 543, 1907.

43 Clark, L. Pierce, and Taylor, Alfred S. True Tic Douloureux of the Sensory Filaments of the Facial Nerve. Cure Effected by Physiologic Extirpation of Genuiculate Ganglion, *J. A. M. A.* **53** 2144 (Dec. 25) 1909.

44 Reichert, Frederick Leet. Tympanic Plexus Neuralgia. True Tic Douloureux of the Ear or So-Called Genuiculate Ganglion Neuralgia, Cure Effected by Intracranial Section of the Glossopharyngeal Nerve, *J. A. M. A.* **100** 1744 (June 3) 1933.

45 Hall, George W. Auricular Neuralgia, *Arch Neurol & Psychiat* **29** 615 (March) 1933.

EFFECT OF EXPERIMENTAL CARDIAC INFARCTION ON RESPONSE TO DIGITALIS

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In 1925 a study was published by one of us (Dr Gold¹) on the tolerance of the cat to ouabain in the presence of coronary occlusion. It was found that within periods up to twenty-four hours after extensive ligation of coronary vessels animals required on the average as much ouabain to cause death as did normal animals. These results were confirmed in a recent study (1934) by Bellet, Johnston and Schecter,² in which the drug was digitalis, the interval between the ligation and the testing was thirty minutes and the animal used was the dog. These authors extended their study to include chronic experiments, and from them they found that four days after the ligation the tolerance to digitalis had diminished by about 23 per cent of normal but that in from six weeks to six months some recovery of tolerance had taken place (tolerance being reduced about 14 per cent). The latter figure, however, represents an average of results for only four animals with two specimens of digitalis. Two other observations aroused our interest: first, that the reduction in tolerance appeared to be proportional to the size of the infarct and, second, that the cat appeared to behave differently from the dog, for in preliminary experiments it was observed that in the cat no diminution of tolerance to digitalis occurred from six to eleven days after ligation of a coronary vessel.

Both of these observations were significant and appeared to be in need of stronger support. An opportunity presented itself to look into this matter in the course of another investigation,³ in which a large number of cats had survived for three weeks after acute cardiac infarction. The effect of digitalis under these conditions was investigated, and the results form the subject of the present report.

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1 Gold, H. Action of Digitalis in the Presence of Coronary Obstruction, *Arch Int Med* **35** 482 (April) 1925

2 Bellet, S., Johnston, C. G., and Schecter, A. Effect of Cardiac Infarction on the Tolerance of Dogs to Digitalis, *Arch Int Med* **54** 509 (Oct.) 1934

3 Gold, H., Travell, J., and Modell, W. The Effect of Theophylline with Ethylenediamine (Aminophylline) on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, *Am Heart J* **14** 284 (Sept.) 1937

EXPERIMENTAL METHOD

Experiments were carried out on fifty cats. The same tincture of digitalis was used in all the experiments.

The method of testing tolerance was uniform. All operations were performed with the animal under local anesthesia. The tincture was diluted twenty times with physiologic solution of sodium chloride and injected into the saphenous vein from a buret until there was cessation of the heart beat, which was always preceded by a convulsion. The solution was administered by the interrupted method, a dose equivalent to approximately 2.5 per cent of the cat unit being injected at intervals of two minutes.

An electrocardiogram (lead II) was taken just before the injection of each 2.5 per cent fraction.

The blood pressure throughout the experiment was recorded from the carotid artery by a mercury manometer. Clotting was prevented by the occasional injection of about 0.2 cc of a 5 per cent solution of chlorazol pink into the system near the cannula.

The animals with cardiac infarcts were those included in another investigation, and the details of the technics, as well as the condition of the animals, were described in that report.⁴ Briefly, the coronary vessel that was ligated was the left circumflex artery, except in two instances. The left descending artery was ligated in one and the left circumflex branch together with the right coronary artery in the other. Detailed autopsies were made in all cases. The area of the infarct was measured with a planimeter after reproduction of the outlines on glass or paper.⁵

RESULTS

The effects of digitalis were compared for three groups of cats.

- Group A. Animals three weeks after ligation of the coronary artery (table 1)
- Group B. Animals three weeks after a control operation, in which the coronary vessel was exposed but not ligated (table 2)
- Group C. Animals on which no operation was performed

Influence of Infarction on Various Actions of Digitalis—A Fatal Dose. The average fatal dose of the tincture, determined by the technic of injection employed in this study, was 0.82 (0.51 to 1.05) cc⁴ per kilogram for the normal animal (nine cats). The average body weight for this group was 2.65 Kg, and the average period of injection was seventy-one minutes.

In groups A and B, both comprising animals that had been operated on and had been kept under special conditions for three weeks, it was necessary to take account of the change in body weight in calculating the fatal dose. The tolerance of an animal to digitalis changes with a loss of weight, but it has been found⁵ that the fatal dose per kilogram after starvation is the same as that for the normal animal when the total dose

⁴ It is interesting to note that a slight modification of the technic did not appreciably change the size of the fatal dose, for an essentially similar result was obtained (0.85 cc) as the cat unit of this specimen in an assay carried out on eight cats a few months previously, the injection in that case having been continuous and the average duration of the injection having been sixty minutes.

⁵ Gold, H. Digitalis Elimination, Arch Int Med 32:779 (Nov.) 1923.

TABLE 1—Results for Twenty-Nine Animals Three Weeks After Ligation of Coronary Artery

Cat No	Fatal Dose of Tincture of Digitalis, Cc per Kg	Size of Infarct, Sq Cm	Mean Blood Pressure Before Digitalis, Mm Hg	Change in Weight, Percentage	Dose Causing Ventricular Ectopic Rhythm, Cc per Kg
1	1.13	2.65	183	+ 3.4	0.19
2*	0.92	3.68	170	+ 2.3	0.56
3	0.78	5.94	175	— 6.0	0.36
4	0.76	6.39	133	—21.2	0.45
5*	0.73	2.90	120	—14.8	0.35
6*	0.71	3.23	150	—13.3	
7	0.70	4.19	170	+ 7.2	0.36
8	0.66	4.45	159	+ 1.4	0.18
9	0.65	3.74	155	—13.8	0.50
10*	0.63	5.94	153	—13.2	0.43
11*	0.62	6.97	150	+ 7.3	0.24†
12	0.62	5.61	135	—14.2	0.47
13*	0.61	3.23	146	—19.4	0.33
14*	0.59	3.55	146	—14.1	0.42
15*	0.56	5.74	135	—24.5	0.49
16*	0.55	6.90	160	— 6.7	0.30
17	0.54	9.48	154	—13.5	0.29
18	0.53	3.94	133	—16.4	0.42
19*	0.53	6.97	133	—21.1	0.30
20*	0.52	9.81	148	—11.8	‡
21	0.48	3.36	158	—16.3	0.28
22*	0.47	12.84	125	— 0.9	0.38
23*	0.46	5.29	144	—22.0	0.22
24	0.45	6.45		—10.8	0.36
25	0.44	2.58	155	— 6.9	0.37
26	0.43	6.07	161	—16.3	0.24
27	0.42	6.97	135	—15.8	0.29
28	0.37	7.36	155	—19.6	
29	0.36	2.26		— 6.1	0.36
Averages	0.59	5.47	150	—10.9	0.35 (59.3% of M L D)

* Treated with aminophylline

† Ectopic beats were present in the electrocardiogram before the injection of digitalis

‡ Idioventricular rhythm was present in the electrocardiogram before and throughout the injection of digitalis

TABLE 2—Results for Twelve Animals Three Weeks After Control Operation

Cat No	Fatal Dose of Tincture of Digitalis, Cc per Kg	Mean Blood Pressure Before Digitalis, Mm Hg	Change in Weight, Percentage	Dose Causing Ventricular Ectopic Rhythm, Cc per Kg
1	1.15	146	—11.2	0.51
2	0.91	160	— 6.7	0.63
3	0.88	143	— 6.1	0.56
4	0.86	120	—22.2	
5	0.78	185	— 8.9	0.27*
6	0.73	147	—10.7	0.47
7	0.68	156	— 6.4	0.48
8	0.65	173	—17.2	0.38
9	0.63	152	—21.9	0.52
10	0.63	143	—30.7	0.23
11	0.62	151	—17.9	0.48
12	0.54	155	—16.4	0.41
Averages	0.76	155	—12.2	0.45 (59.2% of M L D)

* Ectopic beats were present in the electrocardiogram before the injection of digitalis

required is divided by the average of the original and the new body weight. This method of calculation was employed for the animals of groups A and B in order to exclude a change in body weight as a factor in any alteration in tolerance.

The average fatal dose for twelve animals three weeks after the control operation without ligation of the coronary vessel (group B) was 0.76 cc per kilogram (table 2), or 7.4 per cent below that for the normal animals. This figure, however, is not significant, because it is

TABLE 3—*Summary of Results After Control Operation and Ligation*

Operative Procedure	Average Body Weight, Kg	Loss of Body Weight, Percentage	Mean Blood Pressure Before Digitalis, Mm Hg	Period of Injection, Min	Dose Causing Ventricular Ectopic Rhythm, Cc per Kg	Fatal Dose of Tincture of Digitalis, Cc per Kg	Tolerance to Fatal Action of Digitalis, Percentage of Normal
Control operation (12 cats)	2.84	12.2	155	68	0.45	0.76	92.6
Ligation of coronary artery (29 cats)	2.93	10.9	150	53	0.35	0.59	72.0

TABLE 4—*Comparison of Results Three Weeks After Ligation of Coronary Artery for Animals Treated and Not Treated With Aminophylline*

	Averages for Groups	
	Not Treated (16 Cats)	Treated (13 Cats)
Average body weight, Kg	2.96	2.89
Loss of body weight, percentage	10.3	11.7
Size of infarct, sq cm	5.10	5.94
Mean blood pressure before administration of digitalis, mm Hg	154	145
Period of injection of tincture of digitalis, min	53	51
Dose at which ventricular ectopic rhythm appeared, cc per Kg	0.34* (58% M L D)	0.36* (59% M I D)
Fatal dose of tincture of digitalis, cc per Kg	0.58	0.61
Tolerance to fatal action of digitalis, percentage of normal	70.7	74.4

* The averages were based on the results for eleven animals which were treated and fifteen animals which were not treated with aminophylline.

within the range of variations which may exist in the results of a bioassay made by the use of two different groups of animals.

The average fatal dose for twenty-nine animals with infarction (group A) which were tested three weeks after ligation of the coronary artery was 0.59 cc per kilogram (table 3), representing a reduction of tolerance by 28 per cent of that of the normal animal, or by 22 per cent of that of the group in which the control operation was performed.

The range of tolerance of the animals with cardiac infarction was from 39 per cent below (the most susceptible animal) to 91 per cent above (the most tolerant animal) the average. For the control animals the range was from 34 per cent below to 36 per cent above the average.

It may be seen (table 1) that thirteen of the twenty-nine animals with infarction had been treated with aminophylline in connection with another study³ Each of these had received a daily intramuscular injection, usually 25 mg per kilogram, for twenty consecutive doses, the last dose being given about twenty-four hours prior to the injection of digitalis The results for this group are treated separately in table 4, but since aminophylline appeared to exert no influence on the tolerance to digitalis, the two groups were combined and treated as one for the comparisons in this study The observation that aminophylline does not influence the tolerance to the fatal action of digitalis is in harmony with the findings of Haag and Woodley⁶

B Ventricular Ectopic Rhythm The electrocardiogram provided a means for determining the susceptibility to some of the other effects of digitalis The T wave, the PR interval and the sinus rate were too variable under the conditions of these experiments to be used The data were analyzed, however, (a) with respect to the dose required to produce a ventricular ectopic rhythm and (b) with respect to the influence of digitalis on the displacement of the RT segment

In the control animals (group C) which were not operated on an average of 39 per cent of the fatal dose was required to produce a ventricular ectopic rhythm This amount was smaller than that required to cause the same effect in another study, namely, 54 per cent of the fatal dose for seventy-seven cats⁷ It was also smaller than the figure which we obtained for the other two groups of animals (groups A and B), namely, 59 per cent for each group (tables 1 and 2) When an animal is excited and struggles, ectopic ventricular beats are likely to appear earlier in the course of digitalis poisoning than when the animal is quiet⁸ The animals that were not operated on struggled considerably, the period of assay being the first time that their freedom had been restricted⁹ This may account for the small dose which caused the ventricular ectopic rhythm to appear The animals which were operated on without ligation of an artery provided a more valid control for the group with infarcts The animals in both groups showed relatively little excitement during the injection of digitalis, having grown accus-

6 Haag, H B, and Woodley, J D The Effect of Caffeine and Theobromine on Digitalis Toxicity, *J Pharmacol & Exper Therap* **53** 465, 1935

7 Gold, H, Hitzig, W, Gelfand, B, and Glassman, H A Qualitative Comparison of Various Digitalis Bodies, *Am Heart J* **6** 237, 1930

8 Gold, H, Lieberman, A, and Gelfand, B Mechanism of Production of Subauricular Beats by Digitalis Bodies, *Arch Int Med* **48** 262 (Aug) 1931

9 In two of the nine animals not operated on ventricular ectopic beats were noted before the injection of digitalis, in these the ectopic beats reappeared after the injection of 29 per cent and 32 per cent, respectively, of the fatal dose for each animal (the minimum lethal doses were 0.84 and 0.94 cc, respectively)

tomed to restriction by the frequent taking of electrocardiograms during the three weeks following the operation

The average dose required to produce a ventricular ectopic rhythm in the control animals that had been operated on was 0.45 cc, and in those with infarcts it was 0.35 cc (table 3). In the presence of cardiac infarction, therefore, the tolerance of the animal to this effect of the drug is 22 per cent lower than that of the control. This is the same as the reduction in the tolerance to the fatal action.

C Displacement of RT or ST Segment In the electrocardiograms of human beings digitalis may cause displacement of the ST segment similar to that in coronary thrombosis. This has also been observed for the cat.¹⁰ We found that the change sometimes occurs when the rhythm is normal but more frequently after a degree of poisoning which has induced a ventricular ectopic rhythm. The data were analyzed to determine whether digitalis is more likely to produce displacement of the RT segment in the infarcted heart than in the normal heart. The results show that the displacement was produced in 65 per cent of the twenty control animals and occurred only after the ventricular ectopic rhythm had appeared (chart 1 *D*). In those with infarcts it was about the same, 69 per cent after the ectopic rhythm had appeared (chart 1 *B*), but likewise in 24 per cent (seven animals) a distinct deviation of the RT segment also appeared earlier and occurred during the normal sinus rhythm (chart 1 *A* and *C*). In four of these animals, however, some displacement was present before ligation of the coronary artery, it became much more marked immediately after the operation and subsequently disappeared for a period of days, only to reappear during the injection of digitalis (chart 1 *A*). In other respects this group of seven animals yielded results similar to the average for the entire series of animals with infarction, i. e., the average size of the infarct was 5.35 sq. cm, the average blood pressure before the administration of digitalis was 147 mm and the average fatal dose was 0.60 cc per kilogram. These changes in the "take-off" do not always persist, being present in some beats and not in others, appearing in one tracing and disappearing in a subsequent one (chart 1 *A*). These changes represent the reestablishment, during injection of digitalis, of a temporary effect of occlusion, but their significance remains in doubt.

D Blood Pressure The mean blood pressures for the three groups (groups A, B and C) just prior to the beginning of the injection of digitalis were practically identical, 152 mm for the normal animals, 155 mm for those which had the control operation and 150 mm for those with cardiac infarction.

10 DeGraff, A. C., and Wible, C. L. Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* **24** 1, 1926.

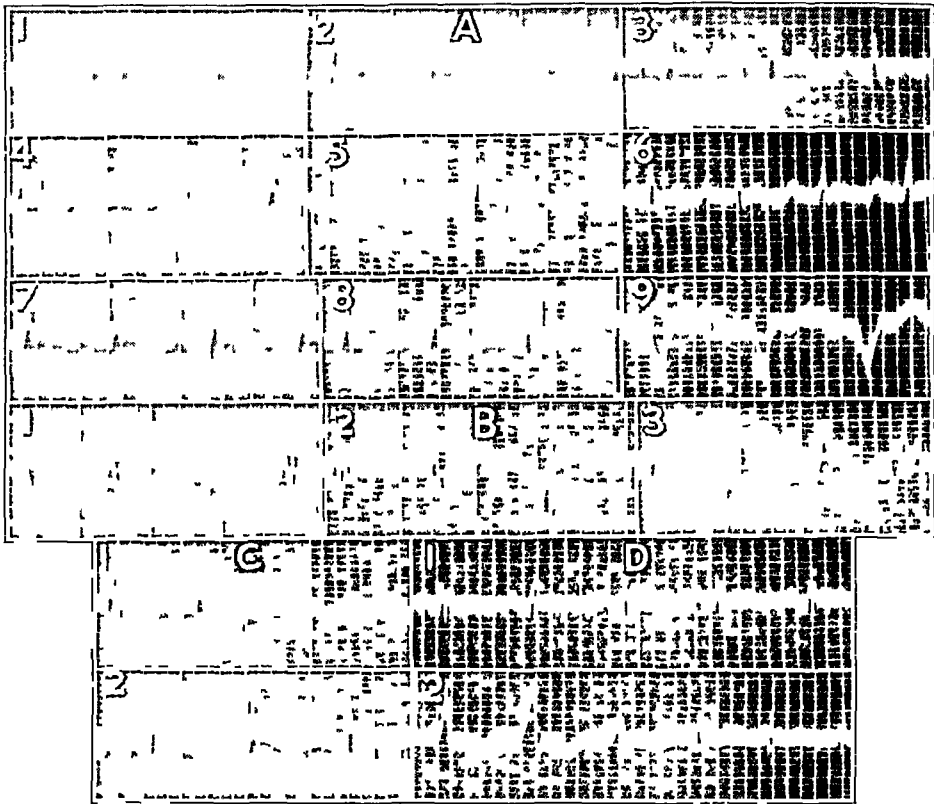


Chart 1—Electrocardiogram (lead II) showing various effects of digitalis on the RT or ST segment *A*, animal with infarction 1, before ligation of the coronary vessel, 2, very high "take-off" seven minutes after ligation, 3, disappearance of displacement of the RT segment on the eighth day after ligation, 4, displacement still absent three weeks after ligation, just before the administration of digitalis, 5, high "take-off" after the administration of 54 per cent, 6, 58 per cent, 7, 66 per cent, 8, 75 per cent, and 9, 80 per cent of the minimum lethal dose. Note the reestablishment by digitalis of the displacement of the RT segment produced by cardiac infarction, its appearance during sinus rhythm and its intermittent character with increasing doses of digitalis. *B*, animal with infarction 1, before the administration of digitalis—spontaneous ventricular tachycardia, 2, after 80 per cent of the minimum lethal dose, 3, high "take-off" after 88 per cent of the minimum lethal dose. Note the absence of the high "take-off" in idioventricular beats before the administration of digitalis and its presence during advanced poisoning, see also *A* 9. *C*, animal with infarction 1, before the administration of digitalis, 2, after 70 per cent of the minimum lethal dose. Note the effect of digitalis in increasing the preexisting displacement of the RT segment. *D*, control animal 1, control tracing, 2, after 81 per cent of the minimum lethal dose. Note the displacement of the RT segment in ventricular ectopic beats, but not in immediately subsequent supraventricular beats.

The typical change in the blood pressure of the cat during the course of the injection of a diluted tincture of digitalis by the technique used in these experiments exhibits two phases (1) a gradual decline and (2) an abrupt collapse

In the normal animal there was a progressive decline of the pressure, which began after an average of 0.25 cc (0.04 to 0.46 cc), or 32 per cent of the fatal dose, and the pressure continued to fall gradually to an average level of about 55 mm (33 to 110 mm), at which it was maintained for a period, after which it fell abruptly to 10 or 15 mm just before the convulsion. The animal then ceased to breathe, or, as was more often the case, several wide fluctuations in pressure occurred before the heart beat and respiration ceased.

The fall in blood pressure did not seem to depend on the ventricular ectopic rhythm, and while a fall sometimes was first seen when the ventricular rhythm appeared, some decline usually occurred while the rhythm was still normal.

In the animal with infarction the changes in pressure were similar to those in the normal animal, the decline beginning after an essentially similar amount of the drug, 0.32 cc¹¹ (0.02 to 0.48 cc, about 53 per cent of the fatal dose for the group with infarction), and continuing downward gradually, but instead of the protracted period of low blood pressure (average, 55 mm) seen in the normal animal during the injection, the pressure in these instances fell abruptly much earlier in the course, from an average level of 90 mm (41 to 128 mm). This applied to the majority of animals, there were some in the group of normal animals (10 per cent) that behaved like those with infarction, and vice versa (33.3 per cent).

The characteristics of animals with infarcts of almost identical average size but with different types of blood pressure curves are illustrated in a comparison of the results for two groups, one of nine animals (infarct, 4.65 sq. cm) showing normal blood pressure curves, the other of five animals (infarct, 4.58 sq. cm) showing abrupt collapse of the blood pressure from a high level of 120 mm or higher. The first group behaved in other respects practically like normal animals, requiring only 11 per cent less digitalis than normal animals to cause a ventricular ectopic rhythm and 3 per cent less to cause death. The second, on the other hand, required 29 per cent less to cause the ventricular rhythm and 39 per cent less to cause death.

The two phases of the change in blood pressure appear to be due to different mechanisms. The fact that the gradual decline of the blood pressure for the animal with an infarct begins after about the same

11 In view of the great individual variability, we believe that no significance can be attached to the difference between this figure and that for the normal animal.

amount of digitalis as for the normal animal suggests that the gradual fall is due to an extracardiac factor. This progressive decline is interrupted earlier in its course in the animal with cardiac infarction by reason of the greater susceptibility of this animal to cardiac collapse (ventricular fibrillation), which is probably the cause of the secondary abrupt fall in pressure.

Influence of Size of Infarct—A Fatal Dose. The size of the infarct was plotted against the size of the fatal dose of digitalis, and the result is shown in chart 2. By this method of examination a correlation is not clear. Of two animals with the smallest infarcts, one required the largest and the other the smallest fatal dose of digitalis. In two groups representing extremes of deviation from the average fatal dose for the normal animal, i. e., one requiring 97 per cent and the

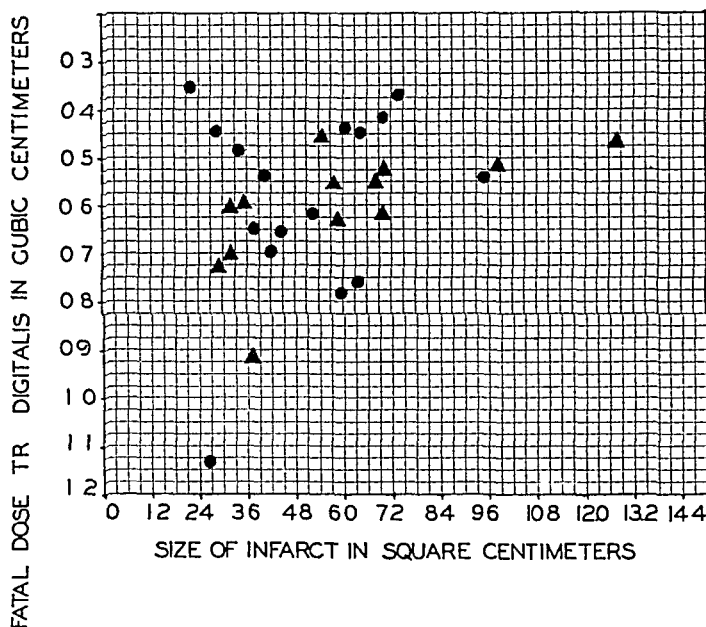


Chart 2—Correlation chart for size of infarct and fatal dose of digitalis. The black triangle indicates animal treated with aminophylline, the black circle, animal not treated with aminophylline.

other 61 per cent of the normal fatal dose, the average sizes of the infarcts were practically identical, namely, 4.65 sq cm for nine animals in the first and 4.58 sq cm for five animals in the second group.

When, however, the small and the large infarcts were grouped separately, a relation was found to exist between the size of the infarct and the size of the fatal dose, as seen in table 5. This table shows that in one group (fifteen animals), in which the average size of the infarct was twice as large as that in another (fourteen animals), the increase in susceptibility was nearly doubled (1.8 times), the average fatal dose being 28 per cent less than that for the control in one and 16 per cent

TABLE 5—*Influence of Size of Infarct on Susceptibility to Digitalis*

Infarcts	Number of Animals	Average Size of Infarct, Sq Cm	Average Dose, Cc per kg	Reduction of Dose, Percentage of Control Dose
A Fatal Dose				
None (controls)	12		0.76	
Smallest	14	3.50	0.64	16
Largest	15	7.29	0.55	28
Smallest	5	2.72	0.66	13
Largest	5	9.29	0.49	36
B Dose Causing Ventricular Ectopic Rhythm				
None (controls)	12		0.45	
Smallest	13	3.48	0.35	22
Largest	13	7.10	0.35	22
Smallest	5	2.72	0.42	29
Largest	5	8.65	0.30	33

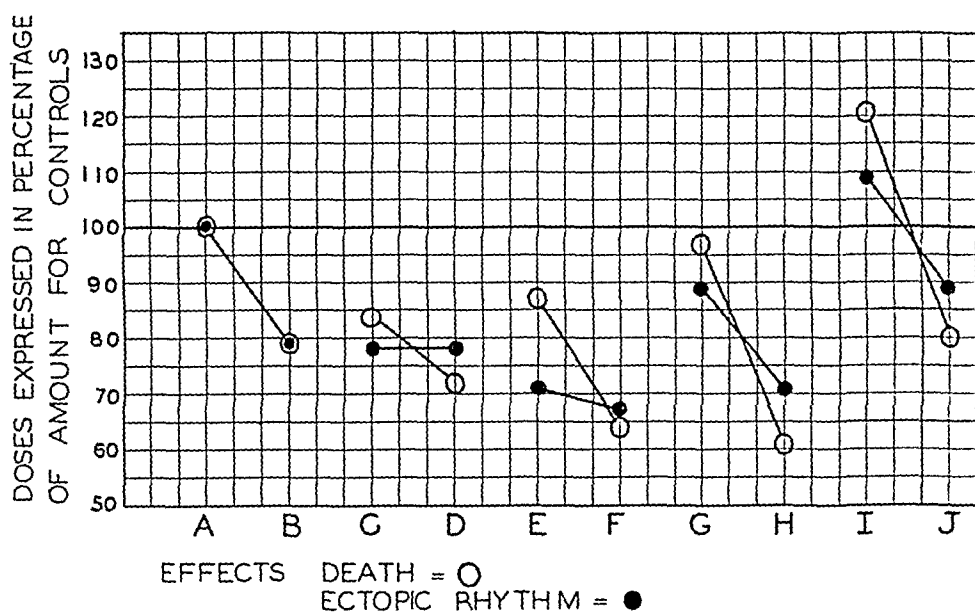


Chart 3—Effect of infarction on the dose required to cause (a) death, indicated by white circle, and (b) ventricular ectopic rhythm, indicated by black circle. The doses are expressed as percentages of the average dose required to produce these effects in the control. AB indicates a comparison of twelve control animals (A), the average dose taken as 100 per cent, with twenty-nine animals with infarction (B). CD indicates a comparison of fourteen animals having the smallest infarcts (C) with fifteen having the largest infarcts (D). EF indicates a comparison of five animals having the smallest infarcts (E) with five having the largest infarcts (F). GH indicates a comparison of nine animals with infarction showing blood pressure curves similar to normal (G) with the group of five showing collapse of the blood pressure from a high level of 120 mm or more (H). The average sizes of the infarcts in G and H were almost identical. IJ indicates a comparison of the five most tolerant animals in the control group (I) with the five most susceptible animals in the control group (J).

less in the other. In two smaller groups, in which the average size of the infarcts of one was about 3.4 times greater than that of the other, the increase in susceptibility was nearly trebled (2.7 times) the average

fatal dose being 36 per cent less than that for the control for the largest infarcts and 13 per cent less for the smallest infarcts

B Ventricular Ectopic Rhythm As may be seen in table 5, the change in tolerance to the ventricular ectopic rhythm shows considerable irregularity and does not appear to depend on the size of the infarct

The relation of changes in tolerance to the fatal action and to the production of the ectopic rhythm is illustrated in chart 3

The abnormal ventricular rhythm which occurs as the result of coronary occlusion is also fairly independent of the size of the infarct It occurred spontaneously in eleven of forty-two cats³ in from two to twenty-one days after ligation of the coronary artery These cases were represented throughout the range of sizes of infarcts, the average for the thirty-one animals without this rhythm being 5.66 sq. cm. and that for the animals with this rhythm being similar, 6.43 sq. cm.

Influence of Degree of Healing of Infarct—There was no relation between the degree of healing seen on microscopic examination of the

TABLE 6—*Relation of Fatal Dose of Digitalis to Degree of Healing of Infarct*

Degree of Healing of Infarct	Number of Cats	Size of Infarct, Sq. Cm.	Fatal Dose of Tincture of Digitalis, Cc. per Kg.
Advanced	4	5.75	0.52
Moderate	15	5.22	0.65
Slight	7	6.29	0.52

infarct and the fatal dose in twenty-six animals in which the infarct was sectioned (table 6). The criteria for the classification of the degree of healing were described in the previous report³

It is interesting to note that all three degrees of healing were present in both large and small infarcts, although one might expect a small infarct to heal more rapidly than a large one. The smallest infarct in our series showed only a slight degree of healing.

COMMENT

The foregoing results show that the cat with a partially healed cardiac infarction requires about 25 per cent less digitalis to cause a ventricular ectopic rhythm than the normal animal and that this change is about the same for infarcts of widely different sizes.

There is approximately the same reduction of the fatal dose. This observation is contrary to that of Bellet, Johnston and Schecter² for cats but practically identical with their results for dogs. In the case of the fatal action the increase in susceptibility varies from 13 per cent in those with a small infarct to 36 per cent in those with a large infarct.

In the animals with infarction requiring a small fatal dose the blood pressure may fall abruptly from a high level of 120 mm. or more rather

than after a period at a low level of about 55 mm as in those requiring a larger fatal dose

Differences in the tolerance to digitalis may involve equally the fatal dose and that causing a ventricular ectopic rhythm, but when the entire group of animals is split up in order to reveal extreme differences in tolerance, the range of change tends to be greater for the fatal dose than for the ectopic dose (chart 3). This applies not only to animals with infarction (*CD, EF, GH*) but also to normal animals (*IJ*)

The mechanism by which cardiac infarction increases the susceptibility to digitalis is not known, but certain facts have thrown light on the following possibilities

- 1 Reduction of the cardiac mass taking up digitalis
- 2 Reduction of the cardiac power to withstand the rapid rate of the ventricular tachycardia
- 3 The providing by the infarct of a region in which digitalis sets up abnormal impulses leading to ventricular tachycardia and fibrillation

The first of these possibilities cannot be effectively defended, as the cardiac muscle takes up an extremely small proportion of the total amount of digitalis administered. Furthermore, perhaps an even larger mass of muscle is excluded from the circulation shortly after ligation of the coronary vessel, and at this time, as shown in other studies, no reduction in the fatal dose is demonstrable. The second possibility also seems unlikely as the sole explanation, as it fails to explain the fact that susceptibility is increased to the ventricular ectopic rhythm itself. This mechanism may play a part, since animals with the larger infarcts tolerate relatively less digitalis after this rhythm has been produced by the drug than do those with the smaller infarcts.

The third possibility is more in harmony with the existing facts. Accordingly, the increased susceptibility to a ventricular ectopic rhythm would be due to the action of digitalis in an abnormal region of the heart from which arise stimuli leading to ventricular tachycardia and fibrillation. This receives support from the fact that the susceptibility to the ventricular rhythm as well as to the fatal action is increased and that an extremely small and a very large infarct may cause approximately the same reduction in tolerance to the ectopic rhythm, indicating that the essential factor is the presence of an abnormal focus rather than its size. The abnormal area from which impulses might arise would not be the region in which the circulation is completely abolished but an area of muscle around or in the infarct in which healing has taken place and in which the circulation is impaired. This is suggested by the fact that the increased susceptibility to the fatal action develops only after a degree of recovery from the complete occlusion, no change

being in evidence shortly¹² after the vessel is ligated. It is conceivable that the abnormally susceptible region is the rest of the ventricle, rather than any special focus in or about the infarct, although this involves the assumption that the hyperirritable state of the ventricle develops during the period of recovery rather than immediately after closure of the coronary vessel, when the strain on the ventricle is probably the greatest.

Clinical Significance—The value of digitalis in coronary thrombosis does not come within the scope of this study. It is well known that relatively few patients with coronary thrombosis require digitalis, but our results lend no support to the belief that the use of digitalis is attended by any special hazards in these cases. The landmarks which have been examined have not appeared to be materially changed. Thus, the range of variations in tolerance, especially tolerance below that of the average for the group, is practically the same as that for normal animals. Also, the ventricular ectopic rhythm, which appears after about 60 per cent of the fatal dose for normal animals, is produced by a similar percentage of the dose that was fatal for the group with infarction. One factor which cannot be investigated in the animal is the range between the full therapeutic and the toxic action (margin of safety). If, by any chance, the susceptibility to the therapeutic action were to remain unchanged, the margin of safety would be reduced, but concerning this we have no data.

As matters stand, the experimental results may be taken to signify that in order to attain the usual objective it would be safer to use about 25 per cent less digitalis for patients with coronary thrombosis than for those without it. The reduction of the dose may be somewhat less for patients with a small infarct and somewhat more for those with a large infarct. Should one fail to take this factor into account when massive doses are given for rapid digitalization, undoubtedly toxic symptoms would result. However, with the slower methods, in which symptoms serve more effectively as a guide to dosage, a 25 per cent diminution in tolerance or its converse, a 25 per cent increase in the dose, might readily escape detection.¹³

SUMMARY AND CONCLUSIONS

In the present study of fifty cats the effect of digitalis on the control animal is compared with that on the animal three weeks after experi-

12 We have no data on the tolerance to ventricular tachycardia shortly after the occlusion, the previous studies having involved consideration of only the fatal dose.

13 Wyckoff, J., Gold, H., and Travell, J. The Importance of Differences in the Potency of Digitalis in Clinical Practice, *Am Heart J* **5** 401, 1930. Gold, H. and DeGraff, A. C. Studies on Digitalis in Ambulatory Cardiac Patients. IV. Newer Principles of Digitalis Dosage, *J A M A* **95** 1237 (Oct 25) 1930.

mental ligation of a coronary vessel with respect to the following points: the fatal dose, the dose necessary to produce a ventricular ectopic rhythm, the effect on the blood pressure, the changes in the RT segment of the electrocardiogram and the degree of healing of the infarct.

Previous studies have shown that within the first twenty-four hours after the experimental production of cardiac infarction the tolerance to digitalis is the same as that of the normal animal (cat and dog).

In the presence of a partially healed infarct the cat (as well as the dog) is more susceptible to digitalis than the normal animal, requiring only about three-fourths as much digitalis as the normal animal to cause (a) a ventricular ectopic rhythm and (b) death.

The larger the infarct, the more susceptible the animal, but many exceptions to this rule were observed, and some of the most susceptible animals had the smallest infarcts.

Treatment with aminophylline appeared to exert no effect on the tolerance to digitalis in cardiac infarction.

There is some indication that digitalis may cause displacement of the RT segment in the electrocardiogram more readily in animals with cardiac infarction than in the normal animal.

Differences in tolerance may involve equally the fatal dose and that required to cause a ventricular ectopic rhythm, but the range of change tends to be greater for the former than for the latter. This appears to be true of differences in tolerance among apparently normal animals, as well as among those with cardiac infarction.

The facts indicate that increased susceptibility to digitalis in cardiac infarction may be due to a change in the properties not of the whole heart but of an area with impaired circulation within the zone of the infarct, from which abnormal impulses arise as the result of the administration of digitalis and precipitate ventricular tachycardia and fibrillation.

SUBCUTANEOUS ADMINISTRATION OF OXYGEN

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AND

M HERBERT BARKER, M D

CHICAGO

The subcutaneous administration of oxygen first became popular in Europe after the introduction of a machine built by Dr Bayeux,¹ of Paris. Since then there has been much controversy as to the value of this form of therapy, but little attention has been paid to it in America and England until recently. The workers on the subject can readily be divided into two groups: first, those who believe its use to be of value, basing their conclusions on clinical observation unconfirmed by laboratory procedure, and, second, those who declare it to be useless, their conclusions being based entirely on experimental data.

One cannot deny that if clinical benefit is seen from the injection of oxygen subcutaneously, there must be some basis for its use. Workers claim benefit from its use in such diverse conditions as distemper, burns, pneumonia, postoperative nausea and vomiting, heart failure, pulmonary tuberculosis, thrombosis and embolism, pulmonary edema, toxemia, septicemia, uremia, convulsions and asphyxia of the new-born, in fact Simon² and Kirk³ gave as indication for its use any condition complicated by symptoms of anoxia and asphyxia. Most of those in favor of the administration of oxygen subcutaneously admit that the amount injected is not sufficient to alter materially the oxygen content of the blood, yet in all the conditions enumerated what other common factor

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The Linde Air Products Company donated the oxygen and nitrogen for use in these experiments

This work was made possible in part by a grant from the Council on Physical Therapy of the American Medical Association

Read before the Section on Pathology and Physiology at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N J, June 11, 1937

1 Bayeux, R. Bull Acad de med, Paris **87** 176, 1922

2 Simon, Oliver B. Clin Med & Surg **40** 155, 1933, Anesth & Analg **13** 233, 1934

3 Kirk, T S. Brit M J **2** 195 (Aug 4) 1928

is there that can be benefited by the subcutaneous administration of oxygen?

As we are particularly interested in the use of this method in pneumonia, in which great benefit is claimed, we shall confine ourselves to a discussion of this subject

Kirk³ said that the early administration of oxygen subcutaneously in cases of acute lobar pneumonia gave uniformly good results, the crisis coming on rapidly. He showed charts to demonstrate this. He cited one instance in which he gave a large dose of oxygen subcutaneously four hours before death to a patient suffering from double pneumonia. At postmortem examination, four hours later, there was no rigor mortis, and the blood that issued from the anterior cutaneous incision was bright red. There was no statement as to the presence or absence of cyanosis before death. Considering the rapidity with which blood, even after death, takes up oxygen, one must be skeptical of this observation. Kirk said he believed that oxygen given subcutaneously acts by helping to kill the pneumococcus and at the same time by counteracting the toxemia. He stated that "subcutaneous injections of oxygen, besides being of great use in cases of pneumonia, are of value in all cases of anoxia."

Lipkin and his associates⁴ studied the effect of the subcutaneous injection of oxygen on the hemolytic, complimentary and specific antibody potency of the serum of dogs. They found the first two values to be reduced and the last to be raised from sixteen to fifty days after the commencement of such treatment. However, the alteration in the agglutination titer is of such small magnitude as hardly to warrant this conclusion. Their experiments were carried out on five dogs (two being controls), and the amount of oxygen given daily varied from 10 to 30 cc per kilogram of body weight. They suggested that the injection of oxygen might be of practical use in the treatment of acute and chronic diseases and for the preparation of more potent specific serums. However, in the treatment of pneumonia the disease had run its course before the injection of oxygen could have had any of the effects mentioned.

It is of interest here to note that Evans⁵ reported on one patient with pneumonia whose cyanosis failed to clear up completely with the nasal administration of oxygen but did so when oxygen was given subcutaneously. Neither the amount of oxygen in the blood nor the amount of oxygen injected was reported.

Simon² remarked that the efficacy of the subcutaneous administration of oxygen in pneumonia seems unbelievable, considering the large

4 Lipkin, J. J., Podvalny, P. B., and Grintzevic, O. M. *Journal of bacteriology and immunology* **13** 661, 1934.

5 Evans, John H., and Durshordwe, C. J. *Anesth. & Analg.* **11** 193, 1932.

amount required by the inhalation method. To explain this he said that in pneumonia the amount of deficiency in oxygen saturation is presumably in proportion to the difference between the supply and the demand and that this is usually a small amount. He claimed that in pneumonia distress and anxiety are relieved after the administration of oxygen subcutaneously.

In support of the contention that oxygen injected subcutaneously is readily utilized by the body, he measured the basal metabolic rates of two hyperthyroid patients before and directly after the injection of 200 and 300 cc., respectively, of oxygen subcutaneously. The latter amount caused the basal metabolic rate to fall as much as 18 per cent in ten minutes, the return to the former level taking as long as ten days. He said, "This indicates that there is an indirect effect on the anoxia due to the slowing of the metabolism processes." However, if one takes into consideration the ends that normally arise in determining basal metabolic rates, these observations must be regarded as of doubtful value.

It may be assumed, then, that Simon concluded that the subcutaneous administration of oxygen actually compensates for the disproportion between the supply and the demand of oxygen. This disproportion must be small indeed, considering that in the normal animal subcutaneous oxygen is absorbed at the rate of 0.6 to 1.2 cc. per minute.⁶ Singh⁶ and Campbell⁷ also found that the absorption of oxygen became nil, or nearly so, at the end of from one to one and a half hours after the injection because of the lowering of the tissue tension of the injected gas. However, these experiments were carried out on the normal animal, and presumably if the animal's demand for oxygen were much greater, the rate of absorption from the tissues might be correspondingly increased. With this fact in mind, we carried out the experiments to be described.

In a series of experiments on the effects of anoxia on the chemistry of the blood, reported on elsewhere,⁸ we found that oxygen could be withheld from the inspired air of normal dogs with impunity until a level of from 4 to 4.5 per cent was reached, when critical symptoms of anoxia were noted. Death occurred when there was about 3 per cent of oxygen in the inspired air. At these low levels the oxygen saturation of the arterial blood was found to be approximately 30 per cent. The demand for oxygen at these low levels should be sufficient to lead to utilization of some of the oxygen injected subcutaneously.

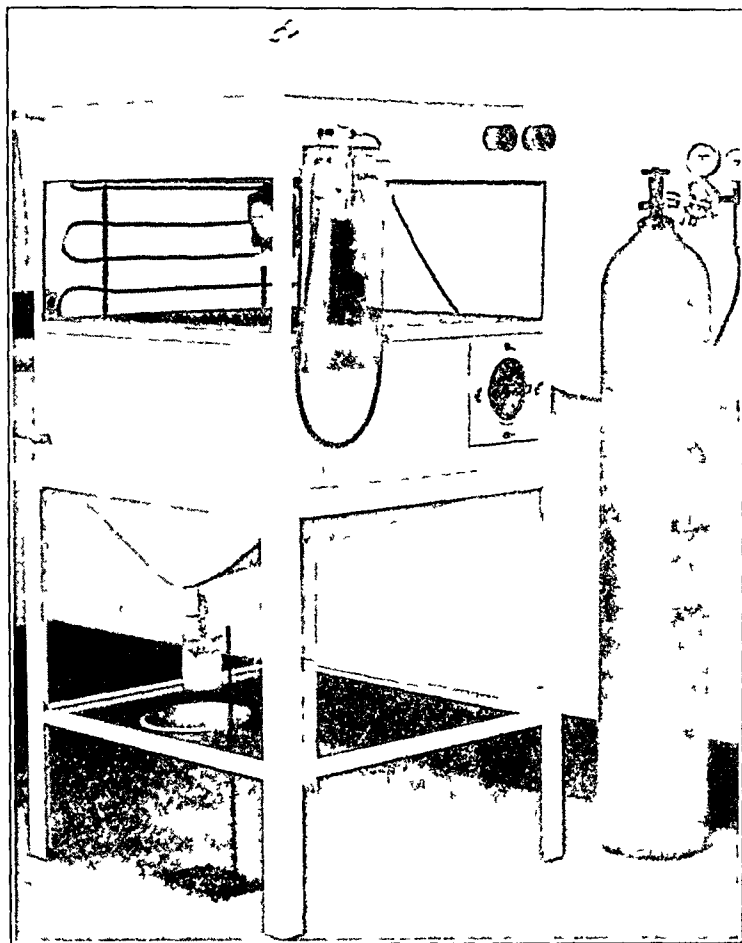
⁶ Singh, I. *Quart. J. Exper. Physiol.* **22**, 193, 1932.

⁷ Campbell, J. A. *J. Physiol.* **59**, 1, 1924.

⁸ Simpson, Thomas, and Barker, M. Herbert. *Studies in Prolonged Anoxia, in Report on Epilepsy*, Ann Arbor, Mich., Edwards Brothers, Inc., 1936, pp. 441-473.

METHOD

To carry out the following experiments we used a miniature oxygen chamber (figure). The chamber is of steel and glass and in two parts. The upper part measuring 2 feet and 6 inches (76 cm) in every dimension, can be raised from the lower part. When lowered it rests on a soft rubber cushion set in a trough in the lower part, this acts as an air seal. Inside the upper part (the chamber proper) and in the left window can be seen a set of cooling coils, and in the upper part at the right side (out of sight) is a tray of soda lime. The Muter "Telaire" apparatus on the right window records temperature and humidity. The various



The oxygen chamber is of steel and glass and measures 30 by 30 by 30 inches (76 cm). It is closed when resting on the sponge rubber in the trough of the steel table, 36 inches (91.5 cm) high. The chamber can be separated from the base by a pulley, which hooks into a ring on the top, thus permitting admission or removal of animals. The bottom of the table is equipped with a trap drain. Note the vents for conditioning the atmosphere, the cooling coils and the instruments for gas analysis. The small trap-door at the right permits feeding, obtaining samples and giving medication, as in the chamber of Thalheimer. If an animal board is placed at this trap, the animal's head can be kept in the chamber in the conditioned atmosphere while the body remains outside, permitting the drawing of arterial blood and other procedure. The chamber accommodates one large dog, two small dogs or cages for twenty-four rats.

parts seen are for admitting gas and for drawing off samples of the contained air for analysis. Between the upper and the lower part is a complete floor of firm fine mesh wire. In the lower part can be seen a drain, which has a water seal at its most dependent point. This provides for the draining away of excreta and condensed water.

At the right side of the upper part can be seen a rubber cuff encircling a circular door, through this the dog's head was inserted into the chamber so that it breathed only the air in the latter when it was necessary to bring the animal's body outside the chamber. The dog's body rested on a trough outside. With this method samples of blood could easily be drawn from the femoral artery without disturbing the dog. Oxygen was administered subcutaneously by means of a two way pump connected with a large reservoir of oxygen. The pressure exerted during the injection of oxygen was estimated and was never greater than that advised by Simon,² i. e., 40 Gm per square centimeter. The concentration of oxygen inside the chamber was lowered by flowing in nitrogen.

We felt that these conditions were entirely satisfactory, since the dogs used were normal and the respiratory apparatus was in no way interfered with. Also, the temperature, humidity and composition of the air breathed could be carefully controlled. Arterial blood was drawn under oil from the femoral artery and immediately analyzed as to oxygen content and capacity by the method of Van Slyke and Stadie.⁹ To perform these experiments it was necessary to anesthetize the dogs. We chose soluble barbitol for the anesthetic because of its slight depressant action on the respiratory center. We also gave it in small doses, i. e., from 150 to 175 mg per kilogram of body weight.

PROTOCOL

In a preliminary experiment, to see if there was any gross evidence of absorption of oxygen from the subcutaneous tissues in the presence of anoxia, we ballooned a dog's skin with as much oxygen as possible, paying no regard to the amount injected. Then we put the dog into the chamber and reduced the oxygen content of the inspired air to 4 per cent in the course of five hours. We could not detect any external evidence of absorption of the oxygen, nor was cyanosis prevented.

In the first experiment, with the dog in the chamber, we lowered the oxygen concentration of the inspired air gradually to 6 per cent over the course of two and a half days, so as to give the dog time to become acclimated to low oxygen tension. At the end of this time the dog was given soluble barbitol (sodium barbitol) in the proportion of 175 mg to 1 Kg of body weight. After the animal had been anesthetized its head was inserted into the chamber, as previously described. Then 1,500 cc of oxygen was injected subcutaneously, and the oxygen content of the inspired air was lowered to 3 per cent over the course of two and a half hours. Blood was drawn from the femoral artery before the start of the experiment as a control at 6 per cent oxygen tension and before and after the subcutaneous administration of oxygen. The dog died.

Table 1 shows that the oxygen content of the arterial blood did not change after the injection of oxygen subcutaneously. Also, we observed at the time that the symptoms of respiration and cyanosis did not alter, nor was there any external evidence of absorption of the injected oxygen, except perhaps in the cervical region. The only difference noted was that the percentage of oxygen desaturation

9 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* **1** 49, 1921

of the arterial blood was less after the injection of oxygen, i. e., 10.8 per cent as compared with 16 per cent before. This, we thought, was due to an error arising in the drawing of the blood, as is borne out by the discrepancy between the degree of anoxia and the percentage of desaturation of the arterial blood. However, to be absolutely certain we repeated the experiment. A second dog was similarly acclimatized after a control study of the oxygen content of the blood and anesthetized with soluble barbital. When the oxygen content of the inspired air was 5 per cent, arterial blood was drawn, and 896 cc of oxygen was injected subcutaneously, then at the end of two and one-fourth hours arterial blood was drawn again, the oxygen content of the inspired air being maintained at 5 per cent during this period.

Table 2 shows that the oxygen content of the arterial blood remained the same before and after the subcutaneous injection of oxygen. The symptoms,

TABLE 1—Data for the First Dog

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desatu- ration, %
	21	20.20	21.66	6.7
		20.31	22.17	8.4
	6	16.71	20.74	19.3
	5	21.05	25.05	16.0
Before injection of oxygen	5	21.05	25.05	16.0
After injection of oxygen	5	20.31	23.90	10.8

TABLE 2—Data for the Second Dog

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desatu- ration, %
	21	18.51	18.93	2.2
		17.43	18.87	7.6
Before injection of oxygen	5	8.16	19.96	59.1
After injection of oxygen	5	8.16	19.52	58.2

respirations and cyanosis did not improve, in fact, the respiration became deeper and more labored, and again there was no external evidence of the utilization of the injected oxygen. Since the percentage of desaturation of the arterial blood remained unaffected, the observation in the first experiment was in all probability a technical error. There remained the questions as to whether the acclimatization of the dogs affected the experiment and as to whether the oxygen levels were too low for absorption of the injected oxygen to take place. To answer these questions, in the next experiment we drew a control sample of arterial blood and then anesthetized the dog as before with soluble barbital. The dog's head was placed in the chamber, and the oxygen content of the inspired air was reduced to only 8.6 per cent in three hours. Arterial blood was drawn from the exposed femoral artery, and then 1,250 cc of oxygen was injected subcutaneously. At the end of two hours another sample of arterial blood was drawn, the oxygen content of the air remaining constant at 8.5 per cent during this period.

Table 3 shows that the oxygen content of the arterial blood did not alter and that the percentage of desaturation was not materially affected. There was

little if any absorption of the injected oxygen, judging by the external appearances and crepitus of the subcutaneous tissues, nor did the symptoms and cyanosis alter. The dog winced and groaned as the oxygen was being injected, and the respirations became deeper, but we assumed that this was entirely reflex.

As we had not met with success in the previous experiments, it was deemed advisable to evaluate the relative merits of oxygen administered subcutaneously and by inhalation. The dog used in the last experiment was put into the chamber after having had approximately 1,200 cc of oxygen injected subcutaneously and the attempted injection of an additional 200 cc intramuscularly. The oxygen tension in the chamber was lowered to 7 per cent in the course of three and three-fourths hours and to 3 per cent in the subsequent hour. At a tension of 45 per cent of oxygen in the inspired air the dog was restless, cyanosed and extremely dyspneic, and at a tension of 3 per cent it was unconscious and about to die, in spite of the large volume of oxygen present subcutaneously. The respiration slowed and finally ceased, and at this point the dog was taken out of the chamber. He took two or three breaths, and the mucous membranes, which were black, turned bright red. At this point arterial blood was drawn, and the oxygen content was found to be 10.3 per cent. On referring to table 3,

TABLE 3—*Further Data for the Second Dog*

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desaturation, %
	21.0	18.98	21.24	10.6
Before injection of oxygen	8.5	10.33	19.00	45.6
After injection of oxygen	8.5	10.24	19.32	47.0

which presents data for the same dog, it is found that an arterial oxygen content of 10.33 per cent corresponds to a concentration of 8.5 per cent of oxygen in the inspired air. The dog was unconscious for about fifteen minutes, but he subsequently recovered and was perfectly well the next day.

RESULTS

This experiment shows how rapidly the blood takes up oxygen from the air when the need for it is great. Surely this indicates the marked advantage of the inhalation over the subcutaneous method of administering oxygen if adequate pulmonary surface is available when oxygen is urgently needed. The oxygen in the dog's tissues and muscles, although far in excess of that used clinically for human beings, was totally inadequate, whereas a few breaths of ordinary air was sufficient to restore the animal. It seems evident from these experiments on normal anesthetized dogs that at the time when one would most expect subcutaneous oxygen to be utilized, there was no supporting evidence from symptomatology and oxygen determinations. Other workers¹⁰ have stated similar conclusions.

¹⁰ Spehl, P., and Lemort, A. C. *Compt rend Soc de biol* **98** 1262 (May 4) 1928. Davies, H. W., and Rabinovitch, M. *J Physiol* **64** \\\viii, 1927.

COMMENT

Since the volume of oxygen given to the experimental animals was far in excess of that advised for human beings, it is probable that when there is a severe degree of anoxia, such as is encountered in pneumonia oxygen given subcutaneously cannot materially effect the oxygen content or the percentage of oxygen desaturation of the arterial blood, in other words, its benefit, if actual, is not derived from its power to oxygenate the blood.

If this is so and if the rate of absorption of oxygen from the subcutaneous tissues is so slow, it is difficult to conceive what benefit this method can have. Even if the oxygen somehow neutralizes the toxins in pneumonia, as was suggested by Kirk, why may the subcutaneous injection of oxygen seem to be of benefit in other divers conditions, such as heart failure, in which presumably toxemia is absent? The work of Lipkin and his associates⁴ raised the question of the stimulation of the formation of specific antibodies following the subcutaneous injection of oxygen. This is not likely to be a factor in pneumonia (as stated previously), however, we are investigating this point further. Singh⁶ has shown that the ability of the lungs to saturate blood with oxygen is about fifteen or twenty times greater than that of the whole subcutaneous region. This point is well brought out in our last experiment. Finally, the fact that in pneumonia the percentage of oxygen desaturation of the arterial blood and its response to oxygen therapy are of prognostic significance seems to be overwhelming evidence in favor of the conclusion that the oxygen is of benefit solely for its power to oxygenate the blood. More critical evidence is needed before the subcutaneous injection of oxygen can be accepted as a sole means of combating systematic anoxia. The work presented in this paper does not exclude the possible value of the subcutaneous injection of oxygen in cases of extreme anoxia as an adjunct to other standard forms of oxygen therapy, nor is the treatment of local conditions by injection of oxygen covered.

CONCLUSIONS

Oxygen given subcutaneously to anoxic dogs in amounts far greater than that advised for adult human beings failed to alter the oxygen content or percentage of desaturation of the arterial blood.

No evidence of absorption of subcutaneous oxygen by the anoxic animal was obtained even when it was urgently needed.

The great efficiency of the inhalation method is emphasized by these experiments.

ABSTRACT OF DISCUSSION

DR HENRY C SWEANY, Chicago. I am wondering what the effect is in surgical conditions. This method has been used in thoracoplastic operations

apparently with slight temporary improvement of the dyspnea I wonder how Dr Barker would explain that

While physiologists do not seem to be able to explain this action clinicians seem to observe a temporary improvement after its administration I should like to have some clinical discussion of this subject, if there are any clinicians here who have had experience with it

DR CLYDE BROOKS, New Orleans, La We are indebted to the essayist for an excellent paper From the standpoint of physiology, the result is just what would be expected I am utterly at a loss to see how the subcutaneous injection of oxygen could be of any benefit in a case of pneumonia or any other clinical condition in which oxygen want is an outstanding feature If there is any benefit, it seems to me it must be due to the stimulation of reflexes by the local action of the oxygen or some other similar action

DR VIRGIL MOON, Philadelphia I cannot take this subject up from the standpoint of internal medicine, but perhaps one or two observations from the standpoint of pathologic physiology may be pertinent Tissue anoxia becomes a major feature in many clinical states associated with intoxication after burns, during the course of severe acute infections or after extensive trauma or surgical intervention These conditions may lead to a type of circulatory deficiency usually designated as shock Anoxia is one of the major factors in the vicious circle, a self-perpetuating mechanism by which the circulatory failure becomes more and more marked The circulation becomes progressively less able to maintain delivery of oxygen to the tissues It seems to me that the paper by Dr Barker bears directly on that point One of the major difficulties in breaking the vicious circle and in restoring physiologic efficiency is that of getting oxygen to the tissues The lungs are partially incapacitated by virtue of the engorgement and edema which have developed in them Their function perhaps can be reenforced or aided by the administration of oxygen by some other route I had not thought or heard of the subcutaneous introduction of oxygen as a possible means for accomplishing that purpose Giving oxygen in an oxygen tent and, as has been suggested by Dr Bullowa, by inhalation under pressure have been considered It seems that the introduction of oxygen by the subcutaneous route offers another means of attack on the anoxia which may develop in a wide variety of clinical conditions

DR J H BACON, Peoria, Ill I am not a member of this Section, I am a surgeon Years ago, cows with garget were treated by injecting oxygen through the duct of the nipple, and farmers thought that they noted a definite improvement in the condition of the cows Then later the same method was used for women with toxemia of pregnancy, by injecting pure oxygen into the breasts About twenty years ago I had two patients with eclampsia who were given oxygen, all the breasts would hold, over a period of an hour, both of them seemed to improve and, they both recovered I have not been using this method in recent years because other methods of treatment of eclampsia have been introduced since then

DR M HERBERT BARKER I appreciate these questions because they are the questions that are being raised by many The motive for carrying on this type of experimental work is to try to remove some of the uncertainty, confusion and perhaps delusion from the subject of the subcutaneous administration of oxygen

Members of the medical profession are becoming more and more oxygen conscious, and if the subcutaneous administration of oxygen is an answer to the problem of systemic anoxia, then it is the simplest and least expensive method

of treatment. However, according to the literature and according to the facts brought out in this discussion, so many conditions are reported as being aided by the subcutaneous administration of oxygen that the method does not seem sound. Better physiologic reasons must be found for the apparent benefit in these diverse conditions before the method and the small volume of gas used can be accepted as the explanation.

With regard to the injection locally, which Dr. Brooks has discussed, it is our opinion that nothing but reflex stimulation is the cause of some of the temporary and rather acute benefit that is seen. I am doubtful that this is a good answer, but it is impossible to explain it in any other way as yet. Certainly it is not explained from the standpoint of relief of arterial desaturation. The fact that the average person requires from 300 to 500 cc. of oxygen a minute and the fact that from 300 to 500 cc. is introduced once a day subcutaneously render such a method useless to the patient who really needs oxygen. So if results are being obtained with these small doses, they are being obtained in some other way than by the correction of blood oxygen desaturation, as our work tends to show.

I am anxious to support Dr. Moon's discussion in relation to peripheral vascular states in shock, in coronary disease and in postoperative states. In some institutions, as mentioned by Dr. Waters, it has been found that about 75 per cent of all oxygen is given by surgeons. They find it is of tremendous benefit to their patients postoperatively. I am anxious to have the work that we are reporting not stand in any way against the subcutaneous administration of oxygen in conditions in which it can possibly do any good. My experience has been that there are possible uses for it as an adjunct to the inhalation route, but large doses must be given. Administering from 5 to 15 liters under the fascia lata, where it is under pressure and can diffuse into the muscle and where there is a rich blood supply, has seemingly been of real benefit to the severely anoxic patient, for example, the severely anoxic patient with pneumonia, for whom the inhalation route is not sufficient. A large volume of oxygen may be burned every three or four hours. Such an adjunct volume, administered subcutaneously, is quantitatively adequate to do something for arterial desaturation. But this volume is far larger than is customarily given. I feel that conditions of this sort should be studied further. Certainly local conditions, such as the gas gangrenes and some skin grafts, may be benefited by local injection of oxygen, but these are local conditions, not systemic anoxia.

ROLE OF ANOXIA IN PRODUCTION OF EPILEPTIFORM SEIZURES

WITH STUDIES OF THE ACID-BASE EQUILIBRIUM

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For many years different workers have attempted to show that voluntary hyperpnea can produce seizures in a patient with epilepsy. Numerous theories have been advanced for the mode of action, all of them being connected either with changes in the concentration of specific ions in the blood or with alterations in the acid-base equilibrium. In voluntary hyperpnea a state of alkalosis is encountered. Because of this, Lennox¹ suggested, for the first time, that anoxia may play a part in the production of seizures, in that in alkalosis the blood gives up oxygen less readily, thereby causing oxygen lack in the tissues.

On the basis of this premise it should be possible to predict the occurrence of seizures as the result of voluntary hyperpnea. A review of the literature shows a lack of agreement as to the incidence and mechanism of the production of seizures by hyperventilation or anoxia.² To test the rôle of anoxia in producing seizures Lennox and Cobb caused patients to hyperventilate in air poor in oxygen. Seizures were most readily induced in patients with frequent petit mal attacks, but there

The Linde Air Products Company donated the nitrogen for use in these experiments.

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This study was made possible by grants from the Minnie Frances Kleman Fund and from the Council on Physical Therapy of the American Medical Association.

1 Lennox, W. G., and Cobb, S. *Epilepsy*, Harvard Medicine Monograph, Baltimore, Williams & Wilkins Company, 1928, vol. 14.

2 Fog, M., and Schmidt, M. *Hyperventilation Experiments During CO₂ and O₂ Inhalation in Patients with Convulsions*, *J. Neurol. & Psychopath.* **12**: 14-23, 1931. Baudouin, A., and Schaeffer, H. *L'épreuve de l'hyperpnee*, *Rev. neurol.* **1**: 445-473, 1933. Petersen, C. J. N. *Contribution à la pathogenèse de l'épilepsie et à la genèse d'une attaque épileptique provoquée par hyperventilation*, *Compt. rend. Soc. de biol.* **106**: 580-583, 1931.

was failure to obtain them in patients suffering from grand mal seizures. Lennox¹ found that the degree of anoxia sufficient to induce an attack would be inadequate if the respired air contained an increased percentage of carbon dioxide or if the patient was in a state of acidosis.

The results of anoxia depend on its degree, suddenness of production and duration.³ If the oxygen deficiency is of a sufficient degree the acid products formed in the tissues pass into the blood and overcome the normal alkalinity, with resulting marked acidosis. Coincident with this acidosis, the respiratory center is depressed, and carbon dioxide in conjunction with oxygen is necessary to stimulate it. This change of state from one of pure anoxia to one of asphyxial acidosis occurs when the oxygen content of the respired air is reduced to 8 per cent.^{3a} In conditions of moderate anoxia, the bicarbonate level of the plasma falls, the decrease being accompanied chiefly with an increase in the chloride content of the serum and partly by an increase in the protein content. The p_{H} increases moderately. In some cases there may be a diminution in total base so as to help compensate for the loss of carbon dioxide by hyperventilation. There is a reduction in the phosphate content.⁴ If the anoxia is carried further, acids, such as lactic acid, accumulate in the blood, the p_{H} falls and the bicarbonate content of the plasma diminishes markedly. This is the condition of asphyxial acidosis.

Thus, in anoxia there are definite changes in the acid-base equilibrium which are not seen in epilepsy before or after a seizure.⁵ During an attack there is a state of acidosis which is similar to the asphyxial acidosis of severe anoxia.⁶ In an epileptic seizure, however, the acidosis is the result and not the cause of the attack. One must not lose sight of the fact that in the space of a few minutes the acid-base equilibrium may be totally disturbed, as in voluntary hyperventilation.

3 (a) Haldane, J. S. Respiration, New Haven, Conn., Yale University Press, 1922, p. 129. (b) Barcroft, J. Anoxaemia. *Lancet* **2**: 485-489 (Sept. 4) 1920.

4 Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C. Total Acid-Base Equilibrium of Plasma in Health and Disease. IV. The Effects of Stasis, Exercise, Hyperventilation, and Anoxemia, and the Causes of Tetany, *J. Biol. Chem.* **67**: 175-218, 1926.

5 Rossier, P. H., and Mercier, P. Etudes sur l'équilibre acide-base du sang. Epilepsie et alcalose, *Arch. internat. de méd. exper.* **6**: 411-421, 1931. Dautrebande, Lucien. L'équilibre acide-base du sang dans l'épilepsie, *Compt. rend. Soc. de biol.* **94**: 133-135 (Jan. 22) 1926. Fletcher, R. I., and Peden, O. D. Note on Blood Chemistry in Epilepsy, *Lancet* **1**: 1382-1384 (June 15) 1935. Bjure, A. Is There Any Connection Between Epilepsy and Reaction of Blood? *Acta med. Scandinav.*, supp. 34, 1930, pp. 131-138.

6 McLaughlin, F. I., and Hurst, R. H. Acid-Base Equilibrium of Blood in Epilepsy, *Quart. J. Med.* **2**: 419-429, 1933.

A review of the literature caused us to feel that the nature and short duration of the experiments reported, the apprehension of the patient, the frequent occurrence of phenomena of motor excitation, fainting spells and the beneficial effect of carbon dioxide in reducing the incidence of seizures cannot be ascribed to anoxia per se. Therefore, we decided to subject patients with epilepsy to the effects of prolonged anoxia to see at what percentage of oxygen tension in the inspired air we could, if possible, induce seizures.

METHOD

A double oxygen chamber was used for these experiments, but nitrogen instead of oxygen was pumped in to reduce the oxygen content of the inspired air. The patients (thirteen in all) lived in the chambers and had much freedom. They were allowed to get up and walk about, and as there was a communicating door between the two chambers they could talk to each other, play cards and relieve the monotony in other ways. The humidity, temperature and oxygen content of the air were under perfect control. In other words, the patients were free from the apprehension that must occur in any rebreathing experiment. This, we feel, was important. In some cases the diet was planned so as to regulate the intake of phosphorus, sulfur and chlorides and to control further the studies of the acid-base equilibrium. A chart of the water balance was kept so that the twenty-four output of the various ions could be calculated and the mineral balance thus determined. The duration of the patient's stay in the chamber was thirty-six hours, except in the case of three patients, two of whom were released at their own request because they felt ill and one who stayed in for four days. As a routine procedure blood was drawn under oil from the radial artery on the day of the patient's admission to the chamber, and then the oxygen content of the inspired air was lowered to 17 per cent and held there for about twelve hours. This was found adequate to prevent "mountain sickness." In the next eighteen hours the oxygen content was lowered gradually to 10 per cent and in the subsequent six hours to as low as was thought safe for the patient, the lowest being 7 per cent. At this point blood was again drawn from the radial artery. One patient, J. A., who was in the chamber four days, respired the following atmospheres: first day, an average of 16 per cent oxygen; second day, 14 per cent oxygen for twelve hours, and 12 per cent oxygen for twelve hours; and third day, 11 per cent oxygen for eighteen hours. In the subsequent five hours the percentage of oxygen was lowered to 9. Considerable difficulty was often encountered in drawing the final specimens because of the collapsed condition of the arteries. For this reason the percentage of oxygen desaturation of the arterial blood recorded in the charts is not as great in some cases as it should be. If the patient had a seizure during his stay in the chamber, arterial blood was drawn immediately. The carbon dioxide content of the air in the chamber never rose above that of the normal atmosphere of a room, even though there was no soda lime in the air circuit. The carbon dioxide content was kept down by continuous dilution with nitrogen. The oxygen of the air in the chamber was analyzed every one or two hours by means of a Haldane analyzer. The blood in all cases was analyzed for the oxygen content, oxygen capacity, hematocrit reading, carbon dioxide, total halide, sulfur, phosphate and total protein contents, and in some cases cholesterol and phenol contents.

The oxygen content of the arterial blood was determined by the method of Van Slyke,⁷ the carbon dioxide content, by the method of Van Slyke and Cullen,⁸ the total halide content, by the method of Whitehorn,⁹ the total protein content, by the combined methods of Howe and Wu and Koch and McMeekin as described by Hawk and Bergeim,¹⁰ the inorganic phosphate contents of the blood and urine, by the methods described by Fisk and Subbarow,¹¹ the inorganic sulfate contents of the blood and urine, by the method described by Hoffman and Cardon,¹² the cholesterol content of the blood, by the method of Bloor, Pelkan and Allen,¹³ the total phenol content of the blood, by the method of Theis and Benedict,¹⁴ the chloride content of the urine, by the method of Vollhard and Harvey,¹⁵ and the bromide content of the blood (estimation), by the method of Wuth.¹⁶

Similarly, six dogs were placed in an oxygen chamber under normal living conditions, and a series of preliminary studies were made to develop a technic and to study the changes in the blood chemistry in the anoxic animal over long periods of time. The oxygen content of the inspired air was lowered to asphyxial levels and in three cases death ensued.

In the cases of the dogs an explanatory note must be offered for the discrepancy between the percentage of oxygen in the inspired air and the percentage of oxygen desaturation of the arterial blood. This was due to the fact that in some instances, because of a few seconds of delay in the drawing of arterial blood, the dog took a few breaths of normal air. Three such breaths were found to be sufficient to raise the oxygen content of the arterial blood far above its previous level. In the case of J. K., there was a small percentage of desaturation of the blood, due to delay.

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PROTOCOLS

We feel that a protocol of each case is necessary to a complete understanding of the results obtained. However, limitations of space prevent inclusion of the results of each determination of the oxygen, carbon dioxide, temperature and humidity of the air in the chamber.

CASE 1—J A was a single man aged 29. At the age of 10 years, while working on a farm, he had his first convulsion. He had two more attacks in the next two years. He was given phenobarbital and for two years had no attacks. For six or seven years prior to this study the attacks occurred at night, and in 1932 they averaged one per week. During 1934 he had only five attacks. There was no objective evidence of organic disease of the nervous system. No seizures occurred while he was in the chamber. However, he suddenly became extremely cyanotic and unconscious, with irregular respiration, periods of apnea and a rapid thready pulse. Artificial respiration had to be resorted to. This occurred on his fourth day in the chamber, when the oxygen content of the air was 9 per cent.

CASE 2—W B, a man aged 35, had one child alive and well. At the age of 33, a week or two after an attack of influenza, he had a minor seizure. Seizures recurred frequently for a month. Then he had a severe sustained tonic convulsion which lasted two hours. At intervals after that he had at times warnings of attacks, attacks of short duration, with a sense of blurring and fogginess, attacks in which weakness of the right lower extremity developed, in which he sank down and got up immediately, and attacks of generalized convulsions. He became irritable, excitable and short tempered. He was operated on for suspected tumor of the brain in 1933, but none was found. After the operation he had attacks beginning with pallor of the face and staring, but no actual convulsions occurred. He had mild hemiparesis on the right. He had an "attack" while in the chamber when there was 14 per cent of oxygen in the inspired air.

CASE 3—R P, a man aged 28, had one normal child 16 months old. The patient contracted syphilis five years before the onset of seizures and received treatment. About six months afterward he had a convulsive seizure. About one and one-half years before the attack he sustained an injury in an automobile accident, being unconscious for a short time and dazed for a couple of hours. After the first attack he had recurrences once a month. Once they ceased for six months, and then for a period of two months he had one attack every week. The attacks began with an aura of "blankness," which was followed by a typical tonic-clonic seizure. There was no evidence of organic disease of the nervous system. No convulsion or attacks occurred during his stay in the chamber.

CASE 4—J K, a married man aged 46, suffered from grand mal attacks from August 1933 to April 1934 and after that had petit mal attacks. In the first attack he had blurring of vision, after which his head turned to the left, his right arm rose up and he turned to the left and fell unconscious. Subsequently he was weak and drowsy. The grand mal seizures ceased after bromide therapy, but he commenced to have petit mal attacks, in which he became mentally confused and speechless but remained conscious, each attack lasting a few seconds. He said that his memory was poorer. There was no objective evidence of disease of the nervous system. He had a questionable attack when in the chamber at an oxygen percentage of 9.

CASE 5—J R, a boy aged 16, was struck by an automobile when he was 7 years old and lost consciousness for thirty minutes. The skull was said to have

been fractured. With the exception of severe headache, there were no immediate symptoms of injury to the brain. One week later he experienced an attack of petit mal lasting a few minutes. Similar attacks occurred at intervals of several weeks. In the four years prior to this study grand mal attacks appeared at the same intervals. His last attack occurred three and a half weeks before hospitalization. He had an attack two days after admission to the hospital. After a short period of confusion his head and eyes turned to the left, and as his body began to turn to the left he lost consciousness and fell. Then a tonic-clonic convulsion ensued. Although no evidence of intracranial injury was found, the history of skull fracture and a focal character of the beginning of the attacks suggested the possibility of a local pathologic condition. He felt as though he were going to have an attack when the oxygen content of the chamber air was at 85 per cent. None, however, developed.

CASE 6—R. R., a man aged 27, who had been married seven years, had one child alive and well. At the age of 19 years, while at work, the patient had an attack beginning with the seeing of bright spots before his eyes. After an interval sufficiently long to permit him to sit down, he lost consciousness. During this period his extremities were rigid, and on regaining consciousness he slept for three hours. For two years the attacks appeared every three or four weeks. During the following year he was free from any form of attack. In 1930 the attacks recurred from about every four to six weeks but caused no loss of consciousness. Only the right upper extremity became rigid, the fingers became fixed in a semiflexed clawlike position and the right side of the face twitched. At the time of this study each attack lasted about thirty seconds. No critical evidence of organic disease was found, but the focal character of the attacks pointed to some local pathologic condition. He had no attack while in the chamber.

CASE 7—F. W. was a man aged 23. At the age of 15, one year after an attack of polyneuritis following the eating of strawberries and immediately after the drinking of two glasses of wine, he slumped in his chair as though asleep. He remained in this condition for an hour and then awakened but continued to feel drowsy. One year later he suddenly fell, losing consciousness. He began to drink alcoholic beverages, and the attacks occurred once a week, then as often as three or four times a day. He was placed under treatment and had no attacks from January 1935 to the time of his entrance into the hospital on March 4. The attacks occurring prior to January were often ushered in with a feeling of puckering of the lips and at times a sense of a peculiar odor. There ensued a sudden loss of consciousness lasting five minutes, during which he would lie in a "limp" state. In addition to these attacks, for about one and a half years he had attacks of automatism, occurring several times a week, until January 1935, after which he had one or two a week. In an attack which occurred in the hospital he wandered to another patient's bed, took a footstool with him, sat on it and started to undress. When spoken to, he regained full consciousness. A significant fact was his statement that he could bring on an attack frequently by playing a trombone. There was no objective evidence of organic disease of the nervous system. He had an attack while in the chamber when the oxygen content of the inspired air was 14 per cent.

CASE 8—E. O., a man aged 36, had one child living and well. During the first year after his marriage, eleven years previously, he had a nocturnal attack. Similar attacks continued to occur about once a week for seven or eight years. After 1930 the attacks occurred in series of three or four a day and then none for three or four weeks. During the month prior to hospitalization he had two

attacks, and while being examined in the hospital he had an attack. He suddenly stopped following directions, lost consciousness, pursed his lips, became cyanotic, had tonic spasms, made pushing movements with the arm and turned the head to the right. After a few minutes he sat up and searched feverishly for some object, uttered a few nonsensical phrases, half climbed out of bed and continued to pluck at the bedclothes and bedsprings, fifteen minutes later he became normal. In another attack he fell over limply on the table, arose and walked about for a few minutes as if in search of something. There were no objective signs of organic disease of the nervous system. He had no attack while in the chamber.

CASE 9—A H, a man aged 39, was married but had no children. He had gonorrhea fifteen years previously. The first seizure, eight to nine years before, occurred when he was in bed. He "wanted to get out and go to work very bad." He did not know what happened. The spells were the same for the next two years, coming on in the night two or three times a year. Four or five years later he had an attack during the day. After that the attacks occurred every two to four weeks, but he did go as long as six months without one. Two or three years before this study was made he began to have an aura, which lasted for a few seconds and consisted of a feeling of faintness and a feeling as if his "eyes were going out", then everything would turn black. It took him from fifteen to thirty minutes to recover. His last attack occurred eighteen months before entry. There was no evidence of organic disease of the nervous system. He left the chamber at his own request after twenty-four hours because he felt unwell. There were no seizures.

CASE 10—A O, a single man aged 18, had an attack while in Sunday school at 6 years of age. He felt weak, faint and dizzy and on going to the fountain for a drink fell limply and was unconscious for two minutes. There were no tonic or clonic movements. Nine years later he had a similar attack at 7 a. m. For a space of a minute or two he had an aura of dizziness and weakness, followed by unconsciousness. He partially regained consciousness and tried to get up, but everything "went black" and he fell back again. He thought he was unconscious for four or five minutes. After that he had no more than three similar attacks. There was no evidence of organic disease of the nervous system. He complained of cramps in the legs after being in the chamber for twelve hours and requested release. He had no seizures while there.

CASE 11—P D, a married man aged 29, had been an alcoholic addict since the age of 12 years. In 1931 while driving a car he "passed out," finding himself sitting in his place a short time afterward. These attacks occurred two or three times a week. During the following year psychic equivalents of seizures developed, during which he was destructive and maniacal. The attacks increased in frequency to one or two a day. Starting in 1933 the attacks began with an aura of *deja vu*, followed by loss of consciousness and a convulsive seizure. In 1933 he had an acute alcoholic psychosis, from which he recovered. There was no objective evidence of organic disease of the nervous system. He was thought to have a psychopathic personality and a convulsive disorder. He had a number of attacks during the period of hospitalization. He had a fugue when in the oxygen chamber, the percentage of oxygen being 15.

CASE 12—D B, a woman aged 33, had one child. At the age of 14 years the patient began to have attacks with turning of the head to the left and then loss of consciousness and tonic-clonic convulsions, followed by vomiting and sleep. They occurred several times a month until she was 25 but diminished in frequency after pregnancy. During a period of three years, while taking 15 grains (0.97 Gm.)

of phenobarbital a day, she had no attacks. Lately, after the attacks had recurred, she thought she was able to prevent the loss of consciousness and generalized convulsions by grasping her head when it began to turn at the beginning of an attack. There was no objective evidence of organic disease of the nervous system.

The condition in this case ordinarily would be classified as idiopathic epilepsy, but attention should be paid to the focal nature of the beginning of the attack. During the period of hospitalization she was given 15 grains (0.97 Gm.) of phenobarbital daily. No attacks occurred while she was in the chamber.

TABLE 1—*Acid-Base Equilibrium of the Plasma (Arterial Blood) of Anoxic Dogs*

Dog	Date	Oxygen Con- tent of Cham- ber, %	Oxygen Con- tent, Vol %	Oxygen Capac- ity, Vol %	De- satura- tion, Vol %	He- mato- crit, Read- ing, Vol %	Total Phenol, Mg per 100 Cc	Chlo- ride, Mg per 100 Cc	Car- bon Diox- ide, Vol %	Inor- ganic Sulfur, Mg per 100 Cc	Inor- ganic Phos- phorus, Mg per 100 Cc	Pro- tein, Mg per 100 Cc
1	2/26*	21.00					2.16	600	40.0	1.66	3.40	6.51
	2/26*	7.00	17.56	19.02	7.70		2.32	564	50.1	1.66	3.30	6.80
	2/26*	5.75	15.76	19.12	17.60		2.76	576	37.2	0.61	4.60	6.51
2	3/15*	21.00	14.44	19.85	27.30†	48.0	3.00	544	51.3	1.42	2.65	7.20
	3/18*	6.00	17.21	22.08	22.10	51.0	3.70	604	14.5		5.10	7.81
	3/19*	6.00	14.90	20.15	26.00	46.3	3.45	580	22.1	5.90		5.68
3	4/12	21.00	20.20	21.66	6.70	44.6	2.40	520	53.2	1.43	3.14	6.42
	4/15	21.00	20.31	22.17	8.40	45.0	1.70	500	44.7	1.78	2.90	7.00
	4/16*	21.00	20.20	20.35	0.70	39.5	1.79	552	33.4	1.51	2.95	6.51
	4/18*	6.00	16.74	20.74	19.30	62.4		536	23.0	3.74		7.20
	4/19*	5.00	21.05	25.05	16.00	50.0	4.16	520	32.4	2.40	2.46	7.81
	4/19*†	3.00	20.31	23.90	10.80	51.0	3.05	508	24.0	2.67	2.28	7.44
4	5/23	21.00	18.51	18.93	2.20	40.5		556	43.9	3.50	3.10	5.51
	5/31*	21.00	16.43	18.87	7.60	46.0		512	41.7		2.60	6.05
	6/ 6*	5.00	8.16	19.96	59.10	43.0		536	28.7	2.94	2.20	6.70
	6/ 6*	5.00	8.16	19.52	58.20	39.0		536	30.5	3.08	2.50	6.51
5	4/ 1	21.00	21.14	21.18	0.20	44.7	1.71	510	49.4	1.58	2.83	6.73
	4/ 2	21.00	20.98	21.00	1.00	45.0	1.76	528	48.5	1.63	2.80	5.86
	4/ 4*	21.00	17.37	17.39	0.10	42.0	2.48	542	50.4	3.70	3.58	6.11
	4/ 6*†	7.00				44.0	1.20	588	28.7	5.60	1.70	7.10
6	3/ 6*	21.00						500	36.2			
	3/ 7*	7.00	21.19	23.92	11.41	52.5	2.52	476	32.4		2.63	7.33
	3/ 7*	8.50						390				
	3/ 8*	8.00	18.51			39.5	2.78	492	37.2			9.02
	3/ 8*	8.50						464	33.8			
	3/ 9*	6.00	17.11	22.30	22.33	42.7	4.65	568	28.7	1.60	3.36	8.28
	3/11*	6.00	17.68	20.84	15.16	45.7	2.90	564	23.0	1.90	5.90	7.81
	3/12*†	5.50	12.13	20.90	42.00	45.3	4.10	576	19.2	0.92	4.95	8.21

* Day spent in the oxygen chamber

† Venous blood

‡ Death occurred

CASE 13—E. W., a married woman aged 41, had had attacks without an aura every two weeks since the onset of menstruation. The spells had become less frequent, the last ones having occurred five months and one month, respectively, before this study was made. Physical examination revealed no evidence of organic disease of the nervous system, and the patient experienced no attack while in the chamber.

RESULTS

We studied the symptomatology in these cases while the oxygen content of the inspired air was gradually lowered. The respiration was labored before the patient became cyanotic, the cyanosis appearing usually at a concentration of 14 per cent of oxygen in the inspired

TABLE 2—*Acid-Base Equilibrium of Plasma (Arterial Blood) and Intake and Output of Chloride, Phosphorus and Sulfur of Human Beings During Anoxia*

Case		Date		24 Hour Period																			
				Output										Intake									
				Oxygen Con- tent of Cham- ber, %	Oxygen Con- tent, Vol, %	Oxygen Capac- ity, Vol, %	De- satura- tion, Vol, %	He- matoc- rit, Vol, %	Total Phe- nol, Mg 100 Cc	Total Hyalide, Mg 100 Cc	Inor- ganic Sul- fur, Mg 100 Cc	Inor- ganic Phos- phorus, Mg 100 Cc	Plasma Pro- tein, Mg 100 Cc	Bro- mide, Mg 100 Cc	Choles- terol, Mg 100 Cc	Car- bon Dio- xide, Vol %	Chlo- ride, Gm 100 Cc	Inor- ganic Sul- fur, Gm 100 Cc	Inor- ganic Phos- phorus, Gm 100 Cc	Vol., Cc	Chlo- ride, Gm 100 Cc	Sul- fur, Gm 100 Cc	Total Phos- phorus, Gm 100 Cc
J A	10/18																						
	10/19																						
	10/20																						
	10/21*																						
	10/22*	21 00																					
	10/23*	11 50																					
	10/24*	9 50																					
	10/25	21 00																					
	10/26																						
	10/27																						
	10/28																						
W B	7/7																						
	7/9	21 00																					
	7/11*	7 00	11 45	21 35	46 40	42 4																	
	7/12*					51 1																	
R P	7/7																						
	7/9	21 00	22 19	22 29		51 0																	
	7/11*	7 00				50 0																	
	7/12*	21 00				44 0	1 68																
J K	4/18*	9 00	18 63	19 87	6 20	44 8	1 38																
	4/19*	21 00				45 0	1 56																
J R	4/18*	8 50	11 58	20 73	44 10	46 5	1 39																
	4/19*	21 00	13 48	13 90	8 20	42 0	1 97																
R R	4/8*	10 00	17 56	20 62	14 84	49 0	1 92																
	4/9*	21 00	15 37	18 80	7 71	43 0	1 70																
F W	4/8*	13 14	17 35	18 80	7 71	47 4	2 20																
	4/9*	9 50	11 84	14 14	16 27	54 0	2 40																
E O	7/29																						
	7/30*	21 00	20 10	20 20		45 4																	
	7/31*	8 50	10 10	20 20	50 00	47 0																	
A H	8/1																						
	7/29	21 00				45 0																	
	7/30*																						
	7/31*																						
A O	8/1																						
	7/16	21 00				47 0																	
	7/17																						
	7/18*																						
P D	7/16																						
	7/17																						
	7/18*																						
	7/19*	21 00				42 0																	
	7/20*	10 00				49 0																	
E W	3/21*	21 00																					
	3/22*	13 50	16 25																				
D B	3/21*																						
	3/22*	13 00	15 97																				

* Day spent in oxygen chamber
† The bromide content of the blood was less than 75 mg per hundred cubic centimeters

air, although in two cases cyanosis was not apparent until a level of 12 per cent of oxygen was reached. Usually, at the level of 14 per cent of oxygen in the inspired air the patient was extremely dyspneic on exertion. He would feel little troubled, but when the oxygen tension was lowered still further, to a level of 9 per cent of oxygen in the inspired air, he invariably became deeply cyanotic, dyspneic and confused. This, we felt, was the critical level below which it would be hazardous to go, for patient J. A., for instance, artificial respiration had to be used. In some cases irregular breathing was apparent at a level of 12 per cent of oxygen in the inspired air. It can be seen that the symptomatology differed in no wise from that seen in normal adults.¹⁷

Not one typical epileptic convulsion was produced in any patient. However, in all cases motor phenomena were observed at oxygen levels corresponding to the asphyxial stage. In one patient a seizure occurred when he was breathing air containing 13 or 14 per cent of oxygen. Two other patients felt as if they were going to have a seizure when the percentage of oxygen had been lowered to 9 and 8.5, respectively, and two other patients exhibited epileptic-like phenomena when there was 15 and 14 per cent of oxygen, respectively, in the respired air. These findings will be described in detail.

The seizure experienced by F. W. while in the chamber occurred at an oxygen level of 13 or 14 per cent. Another patient who was in the chamber at the time gave an eyewitness account. "W. was resting at the edge of his bed, without any guard, when he rose from his pillow and fell to the floor, striking his head first. He quivered a lot for about five minutes, his eyes staring toward the left. He was almost purple." After the seizure F. W. had a severe headache, which lasted about five hours. The noticeable feature of the blood chemistry at the time of the fit was the marked fall in the level of the carbon dioxide content. His roommate, R. R., under identical conditions, had no symptoms. When the oxygen content of the inspired air was lowered still further, F. W. had no seizures, and the carbon dioxide content of the blood rose, as did the chloride content. It seems, then, that he did not adjust well to anoxia. If the fit had been due to anoxia alone, then when the oxygen was lowered further he should have gone into a status epilepticus. An interesting fact is that he was the patient who by playing a trombone could bring on a seizure, which presumably was due to hyperventilation of short duration.

¹⁷ Schneider, E. C. Physiological Effects of Altitude, *Physiol. Rev.* **1**: 631-659, 1921. Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C. Physiological Observations Made on Pike's Peak, Colorado, with Special Reference to Adaptation to Low Barometric Pressures, *Phil. Tr. Roy. Soc., London*, s. B. **203**: 185-318, 1912. Haldane^{3a}. Barcroft^{3b}.

J K, at an oxygen percentage of 9 in the inspired air, felt as if he were going to have a seizure "I felt my mouth twitching, my nerves shaking I could see and hear, but I could not talk, as you know when you asked me questions I felt weak and went into a cold sweat, you had hold of my right arm and so prevented the fit, as this is the one that goes up when I have a fit" To the observer he appeared to be unconscious He was extremely cyanotic, and his respirations were hissing, deep, labored and irregular His teeth were clinched, and his whole body twitched, but there were no clonic or tonic spasms, nor was there involuntary micturition or defecation The eyes were deviated upward The radial pulse was barely palpable He did not complain when a needle was inserted into an artery, but he did when he was recovering Presumably he was unconscious in the earlier period The symptoms—a barely palpable radial pulse, muscle twitchings and low oxygen tension—point to a state of asphyxial acidosis rather than to an epileptiform seizure When the blood was being drawn, some air entered the syringe, thus ruining the specimen for study However, in this study the oxygen content of J R's blood may be used as it was an absolute control

J R was under the same conditions as J K, just mentioned He felt as if he were going to have an attack when the oxygen content of the inspired air was 8.5 per cent He presented symptoms identical with those of J K

Another patient observed that W B had an attack lasting from fifteen to twenty seconds when the oxygen content of the inspired air was 14 per cent W B was staring straight ahead, and his left hand and leg twitched several times

P D, while in the chamber at a level of 15 per cent oxygen in the inspired air, made several short attempts to tear off the handle of the door, working at it for about five minutes He remembered nothing of it afterward Fourteen hours after removal from the oxygen room he had an attack of confusion, combativeness and loss of memory for that period In the chamber he was garrulous, but after a while he seemed to settle down Ordinarily he was a friendly person

Thus, while they were in the oxygen chamber under the influence of moderate anoxia and therefore of alkalosis for a period of thirty hours, there were produced in patients with epilepsy three epileptiform equivalents Two patients thought they were going to have an attack when a state of severe anoxia had been reached This occurred after a stay in the chamber of thirty-six hours

On reference to the table it will be seen that the changes in the blood chemistry recorded during anoxia, both mild and severe, of patients

with epilepsy did not differ essentially from those seen in dogs and from those reported in the literature. Considering the control determinations of the blood chemistry of these patients, we can see no disturbances of the acid-base balance. The total halide content of the blood during mild anoxia varied little in all the experiments, any change being noted in the nature of a lowering. At the same time the total protein content of the serum either remained stationary or showed a rise. Coincident with this the inorganic sulfate content of the blood almost invariably increased, while the phosphate content decreased. This was especially marked in dog 2, in which the inorganic phosphate level of the blood fell to nil and the sulfate content rose to 5.9 mg per hundred cubic centimeters. In the case of dog 6, in which anoxia was prolonged for seven days, a fall of the phosphate level to nil was noted on the fourth day, with a subsequent rise to 4.95 mg per hundred cubic centimeters. At the same time the sulfate level had fallen to 0.92 mg per hundred cubic centimeters. Peters and his associates⁴ observed a similar reduction in the phosphate content during anoxia, which they said was inexplicable as well as unexpected. Koehler and his associates,¹⁸ in reference to the acidosis during severe anoxia, stated that it might be due in large part to a disturbance in the phosphate system, as has been claimed by Bourne and Stehle.¹⁹ In two instances (R. R. and F. W.) when a more marked fall in the bicarbonate content of the plasma was noted, the total halide content increased markedly. This is in accordance with the findings of Peters and his colleagues.⁴ However, in the case of the dogs, even though the bicarbonate content was lowered enormously, down to 14.5 volumes per hundred cubic centimeters, the total chloride content of the blood showed little change and often a lowering. In these cases it is to be noted that the total protein, inorganic sulfate and total phenol contents all showed a rise, whereas the inorganic phosphate level fell. Why the total chloride level should fall we cannot see. It might be suggested that a reaction to anoxia which is prolonged over the course of days differs from that produced more acutely, or it may be that the amount of nonvolatile acids produced was sufficient to compensate for the loss of bicarbonate.

The bicarbonate content of the plasma was not decreased markedly until the asphyxial levels were reached, this being especially well seen in dog 6, for which a level of 19.2 volumes of carbon dioxide per hundred cubic centimeters was obtained. This is in accordance with

18 Koehler, A. E., Brunquist, E. H., and Loevenhart, A. S. The Production of Acidosis by Anoxemia, *J. Biol. Chem.* **64** 313-323, 1925.

19 Bourne, Wesley, and Stehle, R. L. The Excretion of Phosphoric Acid During Anesthesia, *J. A. M. A.* **83** 117-118 (July 12) 1924.

the findings of Henderson and Radloff,²⁰ as is the fact that only at this point did the total phenol content of the body show a marked rise. We are at present investigating this work in the light of the results obtained by Henderson and Radloff.

We are at a loss to explain the rise in the inorganic sulfate content of the blood and the fall in the inorganic phosphate content, which were usually, but not invariably, seen. It may be that these changes are part of the process whereby the sensitivity of the respiratory center is increased to its specific stimulus (Peters and his associates⁴ and Koehler and his associates¹⁸).

No significant change can be seen in the twenty-four hour output of chloride, sulfate and phosphate of the five patients so examined. The calcium and the magnesium content of the diet were low, so that most of the phosphate was excreted in the urine.

In summary, then, we can say that the acid-base balance of patients with epilepsy in the interval between attacks appears to be normal—that they react as one would expect to anoxia, either mild or severe.

The absence of elevation of the chloride content of the blood of dogs in which the bicarbonate content was tremendously reduced seems difficult to explain. The rise in the inorganic sulfate content of the blood and the fall in the organic phosphate content also were puzzling.

COMMENT

We have observed the results of prolonged anoxia in thirteen epileptic patients under what we consider ideal conditions. The patients lived in rooms and were able to walk about and converse with their neighbors. The air breathed was under absolute control as to humidity, temperature and oxygen content. The oxygen content of the inspired air was reduced gradually over the course of thirty-six hours in the case of twelve patients. During the first thirty hours the average oxygen content of the air was 13.5 per cent, and in the subsequent six hours it was lowered to a level which was thought safe for the particular patient, i. e., from 7 to 9 per cent. The preliminary gradual induction of anoxia was used to prevent the undesirable effects of "mountain sickness." The oxygen content of the air breathed by the patient who stayed in for four days was given earlier in this paper.

In no instance did we observe a typical epileptiform seizure. One patient who was breathing an atmosphere containing 13 or 14 per cent of oxygen had an attack the significance of which has been discussed. Two other patients felt as if they were going to have seizures when

20 Henderson, Y., and Radloff, E. M. The Chemical Control of Breathing as Shown in the Acid-Base Balance of the Blood, Under Progressive Decrease of Oxygen, *Am J Physiol* **101** 647-661, 1932.

they breathed air containing 8.5 or 9 per cent oxygen, but, as has been shown, they were both suffering from severe anoxia. Two other patients exhibited epileptic phenomena when the oxygen content was 14 and 15 per cent, respectively. Motor phenomena were observed in every case when the oxygen content of the air was lowered to asphyxial levels. It should be noted that the patient who had a seizure and two others who felt as though they were about to have seizures were all subject to both petit mal and grand mal attacks. However, P. D., although also suffering from major and minor attacks, did not have a seizure.

To satisfy ourselves that the presence of excess bromide in the blood of these patients (they were all under bromide therapy up to a few days before the tests were carried out) was not a factor in the suppression of seizures, the bromide content of the blood was estimated for every patient when he entered the chamber. In only two cases was the bromide level sufficiently high to have prevented spontaneous convulsions. In the remainder it was so low that it could not be detected by the Wuth method.

The previous work on this subject has been carried out as an acute experiment lasting for minutes, with variable results. The patients have been subjected to a procedure which could not help but fill them with apprehension, and instead of the production of a state of uncomplicated anoxia, these patients have in all probability been reduced to an asphyxial condition. It is not to be wondered that great difficulty has been encountered in distinguishing between the symptoms manifested and true epileptic seizures. We have also noted the occurrence of loss of consciousness, intense cyanosis, rapid pulse rate and motor phenomena at these low levels. In the milder but definite grades of anoxia and therefore of alkalosis we have produced three epileptic phenomena only one of which (the fugue) we were inclined to regard as at all definite.

The reaction of these patients to anoxia, as judged by the symptomatology and acid-base balance, was the same as one would expect and in no way differed from that of normal persons or of control dogs.

We feel that the effect of anoxia per se on epileptic subjects under ideal conditions is not a factor in the production of seizures.

SUMMARY

Thirteen epileptic patients have been observed with regard to the effects of prolonged anoxia.

Five epileptic-like phenomena were obtained, we regarded only one as being a definite seizure and one as questionable.

Every patient exhibited excitation phenomena during severe anoxia

The symptoms and acid-base balance of these patients during anoxia differed in no wise from those observed for dogs and normal human beings

The acid-base balance of the patient with epilepsy in the inter-paroxysmal periods appears to be normal

Anoxia per se does not seem to be a factor in the production of epileptic seizures

Dr Lewis J Pollock and other members of the staff of the neurologic clinic assisted in the selection, control and observation of the patients from the neurologic standpoint

Mr W W Davison helped in the management of the oxygen chamber, and Mrs B Van Dyke and Miss S Hart carried out the analysis of the blood

CONGENITAL DEFECTS OF THE PERICARDIUM

HAMILTON SOUTHWORTH, M D

AND

CHARLES SUMMERS STEVENSON, M D

BALTIMORE

Congenital deficiency of the pericardial sac has never been correctly diagnosed during life. It is an anomaly which has aroused the attention largely of anatomists and embryologists. But in spite of its rarity we believe it is not without clinical significance.

The first case reported of absence of the pericardium was that of Realdo Colombo in 1559, but it seems probable in the light of present knowledge that this was merely a case of adherent pericardium. The first indubitable example of the condition was that reported by Baillie in 1793. Since then about fifty other cases have been described, but in many instances the protocols have been scanty and in none has the clinical side of the picture been stressed. The unusualness of the condition is further emphasized by the fact that in 1909 Veisé found only two examples in thirteen thousand necropsy reports and that the case we are about to describe is the first in the series of over fourteen thousand cases in which autopsy was performed at the Johns Hopkins Hospital. The following case is reported because it is the first one in which an adequate clinical description has been available. The literature on the subject is subsequently reviewed.

REPORT OF A CASE

B McD, a 46 year old Negress, was admitted to the medical service of the Johns Hopkins Hospital on March 23, 1936, and died in eight hours. Her critical condition precluded elaborate questioning, but apparently her health had been excellent save for a transient febrile illness with thoracic pain six years before her admission to the hospital. There were no complaints referable to the heart, and though she was not specifically questioned on this point, her family was unaware that she had any cardiac abnormality. Six days before entry she became ill, showing a typical onset of lobar pneumonia, with shaking chill, pain in the right side of the chest and bloody sputum. As her temperature fell, however, the pain radiated around to the precordium, and her physician sent her to the hospital because she was looking worse.

When the patient was admitted the temperature was 101 F (rectal), the pulse rate 130, the respiratory rate 44 and the blood pressure 140 systolic and 70 diastolic.

From the Department of Medicine and the Department of Pathology, Johns Hopkins Hospital and University.

Physical examination showed a well developed Negress who was critically ill. Respirations were rapid and labored, with audible moisture. Slight cyanosis and definite jaundice were noted. She had a cough productive of tenacious, bile-stained sputum. Her psyche was clear, but she was apathetic. Dehydration was marked. The trachea was in the midline, but the heart seemed greatly displaced to the left, with a forcible apex impulse in the posterior portion of the axilla and no extension of dullness to the right of the sternum. The heart sounds were of fair quality, but there was a loud to and fro friction rub along the left margin of the heart, which, though affected by respiration, seemed predominantly cardiac in origin. Signs of consolidation were noted over the lower lobe of the right lung, being most pronounced in the interscapular region, with evidence of resolution below. There were no signs to suggest effusion into the pleura. At the base of the left lung scattered râles were heard, and laterally a pleural friction rub and slight dullness were noted. The abdomen was moderately distended, and the liver was felt 2 cm below the costal margin. The veins of the neck were engorged.

A blood count showed 34,320 leukocytes, with 98 per cent neutrophils. The urine showed albumin (2+) and a few leukocytes. The sputum contained 98 per cent type I pneumococci, and blood culture showed one hundred and twenty-four colonies of the same organism per cubic centimeter. The Wassermann reaction of the blood was 4+. Because of the extraordinary position of the heart a fluoroscopic study was made of the patient in bed. The heart was observed to be greatly displaced to the left and little, if any, enlarged. The pulsations were well seen. A shadow at the base of the right lung suggested pneumonia, but the costophrenic angle was clear. There was nothing indicative of fluid save a tiny layer in the interlobar fissure. The lower portion of the left lung was obscured by the heart, but no evidence of consolidation was discovered.

In spite of the use of type I pneumococcus antiserum, an oxygen tent, digitalis and sedatives, the course was rapidly downhill, and the patient died after eight hours. The clinical diagnosis was lobar pneumonia, bacteremia and pericarditis due to *Pneumococcus* type I, cardiac insufficiency and syphilis. The cardiac displacement remained unexplained, as there seemed to be neither a significant collection of fluid in the right pleura nor massive collapse of the left lung.

Autopsy—The patient died on March 24, and autopsy was performed in four hours.

Gross Examination The body weighed 54 Kg and was 158 cm long. The nutritional state was average.

The abdominal organs showed the usual arrangement, without peritoneal or diaphragmatic anomaly. The spleen was small, and the kidneys bore a few old scars. There was moderate sclerosis of the aorta.

As the anterior mediastinal connection with the sternum was cut from below upward in the routine removal of the sternum, it was discovered that this connection was absent above the level of the third costochondral junction and did not begin again for a distance of about 6 cm, thus forming a window of about that diameter connecting the two pleural cavities (fig 1). Part of the upper lobe of the right lung protruded through the window and was adherent to the upper lobe of the left lung. The heart, covered with fresh fibrinous exudate, lay in the lower half of the left pleural cavity. No layer of pericardium separated it from the anterior wall of the chest, the left lung or the diaphragm. At the apex an old fibrous band, 1 cm in diameter, bound it to the lateral thoracic wall, and the

epicardium was also adherent to the lower lobe of the left lung and to the left dome of the diaphragm. The left pleural cavity contained about 500 cc and the right about 200 cc of thin purulent fluid. The pleural surfaces of both lungs were covered with fresh fibrinous exudate. The two lobes of the left lung occupied the upper half of the left pleural cavity, while the heart lay below them.



Fig 1—Postmortem appearance of the relationship of the heart and the pleural cavities

With the heart lying in the left pleural cavity, nothing was seen that even suggested a remnant of the left half of the parietal pericardium. A mass of fatty tissue formed the lower part of the anterior mediastinum below the interpleural window. The surface of this mass adjacent to the right auricle extended upward to form a partially encircling collar about the base of the heart and

beyond this merged with the left parietal pleura. The heart was not enlarged, and the great vessels showed their usual arrangement. The lateral displacement of the heart had caused no buckling of the aorta or pulmonary vessels. The myocardial walls were of usual thickness and normal appearance. All the valves were thin and delicate. There was slight sclerosis of the coronary arteries.

The upper lobe of the left lung was displaced upward and backward but contained air. The lower lobe, where it was fastened by fresh exudate to the heart, was collapsed but not consolidated. There was uniform gray consolidation of the lower lobe of the right lung. The upper lobe of the right lung contained air, the middle lobe was small and compressed but not consolidated. The lymph nodes at the hilus of the right lung and in the mediastinum above and below the interpleural window were enlarged. Two adenomatous nodules of the right lobe of the thyroid gland lay beneath the manubrium. The course of the two phrenic nerves was along the spinal column just posterior to the base of the heart, they were not involved in the abnormality.

Microscopic Examination. Confluent lobular pneumonia of the lower lobe of the right lung and patchy atelectasis of the lower lobe of the left lung were noted. The pleural surfaces of both lungs and of the epicardium showed a thick layer of exudate containing polymorphonuclear leukocytes. The exudate over the right lung gave evidence of early organization. The adhesive band at the apex of the heart consisted of scar tissue. Sections through the mass in the lower portion of the anterior mediastinum showed ordinary adipose tissue and a few small islands of lymphocytes. The myocardium was normal, sections through the surface revealed epicardium covered with exudate but no evidence of adherent parietal pericardium. There were subintimal thickenings and hyaline patches in the aorta and in the coronary arteries. Sections from the kidneys showed a few healed cortical scars and extensive vacuolation of the epithelial cells. The thyroid nodules were typical adenomas. There were senile changes in the genital organs and chronic inflammation of the urethra.

Culture.—Type I pneumococci were grown from the heart blood.

Pathologic Diagnosis.—The pathologic diagnosis was as follows: congenital defect of the pericardial sac, with the heart lying free in the left pleural cavity, connection of both pleural cavities through the anterior mediastinum, confluent lobular pneumonia in the lower lobe of the right lung, bilateral fibrinous pleurisy with adhesions, fibrinous epicarditis, with adhesions of the heart to the lower lobe of the left lung, to the left side of the diaphragm and to the lateral thoracic wall, scars of the kidneys, with vacuolation of the epithelium, arteriosclerosis and coronary sclerosis, thyroid adenomas, senility of the fallopian tubes and ovaries, and chronic urethritis.

Comment.—Since there was no pericardial sac enclosing the heart, but a common pleuopericardial cavity on the left, it could be said that there was no pericardium and that the heart was entirely surrounded by pleura. However, it seemed more logical, since there was a layer of mediastinum separating the heart from the right pleural cavity, that this represented the right leaf of the parietal pericardium and that it was the absence of only the left leaf of the parietal pericardium that released the heart into the left pleura. Death was the result of the over-

whelming pneumococcic infection, which in the absence of the usual pleural and pericardial barriers spread so as to produce extensive pleuro-pericarditis as well as bacteremia

EMBRYOLOGY

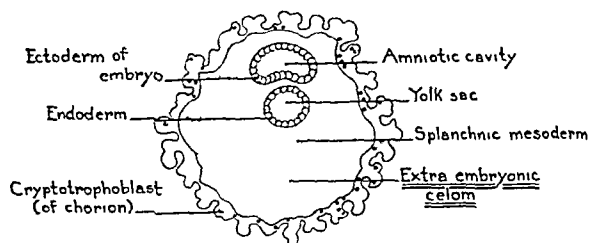
The development of the human pericardium is a complex process the successive steps of which can be briefly summarized as follows. The intra-embryonic celomic cavity first appears as an empty sinus in the mesodermal segment at about the second somite stage (fig 2 *III*). It is an extension into the embryonic mesoderm from the large extra-embryonic celom (fig 2 *I* and *II*), which is found first in the human embryo in the third week. The intra-embryonic celom enlarges and is made up of the large pericardial celom and the two lateral pleuroperitoneal canals (fig 2 *VI*). The latter connect at their lower ends with the extra-embryonic celom.

The ventral wall of the still-paired pericardial celom thickens to form the primordial epimyocardium (fig 2 *IV*). The foregut then buds off from the yolk sac, and the two pericardial celomic cavities fuse, the two endocardial primordia likewise fuse into the one unpaired vessel (fig 2 *V*) which later becomes the heart.

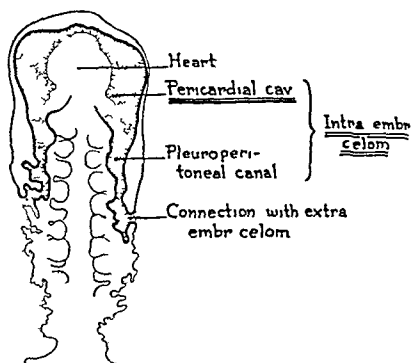
By the fourth week the septum transversum has begun to grow in from the ventral wall (fig 2 *VII*) and it extends dorsally in the midline until it meets the gut. However, it leaves on each side a pleural canal through which the pericardial and peritoneal cavities communicate (fig 2 *VII*). Each canal lies just medial to the common cardinal vein. The lungs begin to bud from the pulmonary ridge (fig 2 *VIII*) and grow into the canal (fig 2 *IX*). Two folds now begin to grow out from the common cardinal vein (ducts of Cuvier) on each side, the ventral fold being the pleuropericardial membrane and the dorsal fold being the pleuroperitoneal membrane (fig 2 *IX*). When these membranes reach the medial wall of the pleuroperitoneal canal on each side of the lung bud, they fuse with it and thus wall off the pericardial and pleural cavities separately from the peritoneal cavity (fig 2 *X*).

Three elements go to make up the diaphragm: the septum transversum, an ingrowth from the body wall and, lastly, the pleuroperitoneal membrane. Any deficiencies in the diaphragm result from the failure of this membrane to close completely over the original opening. Any deficiencies in the pericardial sac are due to the failure of the pleuropericardial membrane to close completely on one or both sides.

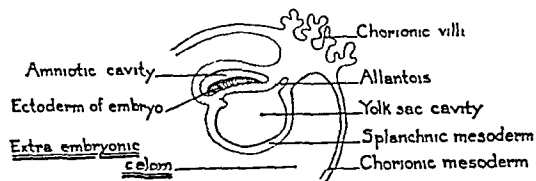
Two theories have been advanced in the attempt to explain why the pericardial defect is generally on the left. The first advanced by Perna and by Plaut, is based on a developmental defect in vascularization. With the formation of the left innominate vein and the azygos



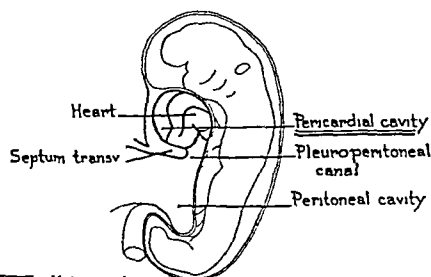
I. 3rd week



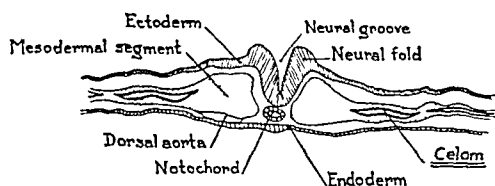
VI. Beg 4th week



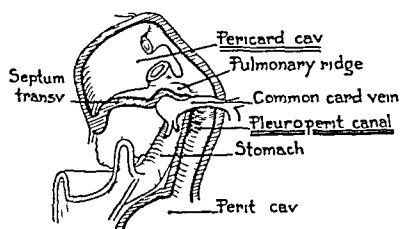
II. 3rd week



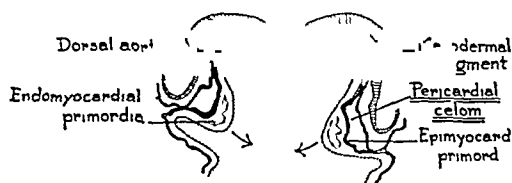
VII. 4th week



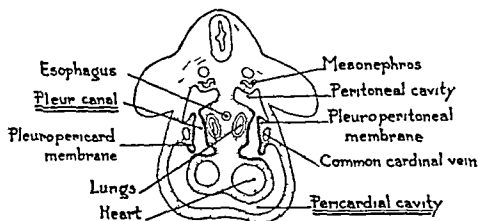
III 7 segment (Chick)



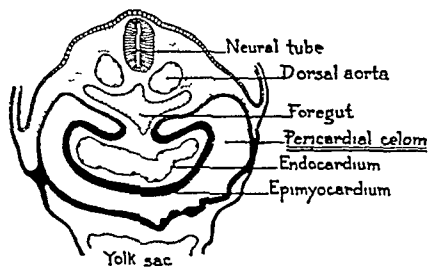
VIII. Late 4th week



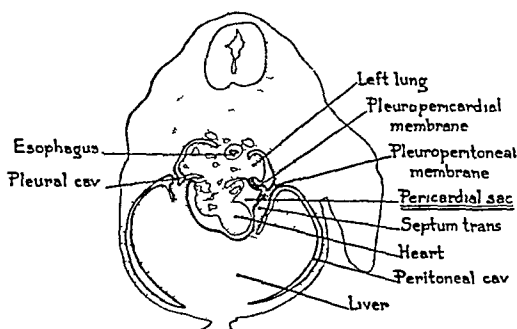
IV 3 1/2 weeks



IX. 5 1/2 weeks



V. Late 4th week



X. Beg 6th week

Fig 2—Development of the human pericardium (diagrams after Arey)

system in the eighth week of fetal life, the left common cardinal vein tends to atrophy and in the adult is represented by only the coronary sinus (Arey). The right common cardinal vein, however, finally develops into the superior vena cava. If, then, the atrophy of the left common cardinal vein were a little premature, incomplete development of the associated pleuropericardial membrane might result from a deficient blood supply. The second theory, advocated by Risel and by McGarry, is based on a primary disturbance in the development of the celomic cavities. McGarry suggested that the defect is generally on the left because the asymmetry of the liver and its rotation during the course of development put the greater tension on the left pulmonary ridge. Moore tends to favor the former of these two theories, because of the comparative rarity of other associated celomic anomalies.

ANALYSIS OF REPORTED CASES

In 1925 Moore was able to find references in the literature to sixty-four cases of pericardial defect, and subsequent authors have accepted his enumeration. According to this count our case would be the seventy-fifth. Moore, however, was able to locate only forty-two protocols, a number extended by Grant in 1926 to forty-six. We have looked up the references of these authors, tracing them back to their sources, and by adding the reports of cases published in the last ten years have been able to locate a total of fifty-four reports of cases. The cases of Realdo Colombo, Tulpio, Littré, Peyer, Lancisi, Brunner and Hoyer have been excluded, as in all probability they were instances of adherent pericardium, as originally stated by Perna. No case was found to be reported in the articles by Greenhow and by Pallavecchio, and the protocols by Memère and by Bieschet obviously refer to the same patient. Descriptions by Feiraires, Weber, Verbeck, Henkel, Wittcke, Phoebus and Shugeninoff could not be traced. Examples of ectopia cordis and pericardial diverticulum have been omitted purposely.

The fifty-four cases thus on record are listed in the accompanying table. Two of them, those of Lawson Tait and Lebec, have been grouped as doubtful because of inadequate or atypical descriptions, a judgment concurred in by Perna. Seven other cases were those of fetuses or new-born infants so disfigured by anomalies as to be classified separately as monsters.¹

¹ Monckeberg's second and third cases have not been so listed because, although one case was that of a new-born infant and the other was that of a 3 week old infant, the cause of death was not given in either case and the failure to describe other anomalies is presumptive evidence that none were present.

Pericardial Defects

I Definite Cases												
No	Author	Date	Sex	Age	Cause of Death	Cardiac Symptoms and Signs	Size of Heart Post Mortem	Type of Pericardial Defect	Pneumonitis	Pleurisy	Adhesions of Heart	Other Anomalies or Conditions
1	Baillie	1793	M	40		0	Very large	Common cavity on left	0	0	0	
2	Walter	1805	M	30				Common cavity on left				
3	Otto	1824	M	Adult				Common cavity on left				
4	Ménière (Breschet)	1826	M	28	Dysentery with perforation	0	Normal	Common cavity on left	0	0	To left lung and diaphragm	Pregnancy
5	Wolf	1827	F	42	Typhus	Angina, mild	Enlarged	Common cavity on left				
6	Curling	1839	M	16	Ascending paralysis	0	Enlarged	Common cavity on left	0	0	To lower lobe of left lung	
7	Baly	1870	M	72	Tuberculosis of lungs and peritoneum	0	Normal	Common cavity on left	Tuberculosis	Fresh exudate to left lung		
8	Bristowe	1877	M	28	Pneumonia		Enlarged	Common cavity on left	Pneumonia	¾ pint (350 cc) of exudate	Old ones to upper lobe of left lung	Jaundice
9	Powell	1868	M		Tuberculosis of lungs and splenic and thoracic nodes			Foramen on left, small	Tuberculosis	Turbid fluid and air in pericardium	0	
10	Peacock	1866	M	75	Aortic valvular disease			Common cavity on left			To left lung	
11	Walsbach	1868	M	22	Pleuropneumonia with exudate	0	Enlarged, bifid	Foramen on left, large, with heart protruding		Purulent pleuro pericardial exudate		Bifid heart
12	Byornstrom	1872	F	40	Colitis, gastric ulcer	0		Common cavity on left			To upper lobe of left lung	
13	Faber	1878	M	51	Acute pleurisy			Common cavity on left		Scrofulinous exudate all over heart and left lung		
14	Charl	1880	M	46	Cirrhosis, tuberculous peritonitis	Only recent, dulled pulmonary second sound	Normal	Common cavity on left				Deep fissure, upper lobes of both lungs

15	Chiari	1880	F	62	0	Enlarged	Common cavity on left	To left lung
16	Chiari	1880	M	60	Pleuropericarditis	Enlarged	Common cavity on left	Pleuropericarditis
17	Pick	1883	W. Young	Pneumonia	0		Common cavity on left	Fresh patches To left lung
18	Hughes	1886	M	33	Advanced tuberculosis of lungs	Normal	Common cavity on left	Lobular pneumonia To left lung and diaphragm
19	Adersen	1887	M	25	Ruptured spleen, bronchopneumonia		Large foramen on left	Serosanguinous effusion
20	Orth	1887			Rupture of aneurysm		Foramen on left	Hemothorax and hemothorax
21	Bovall	1887	F	28	Herniation of heart through defect	Symptoms of pulmonary embolism	Foramen on left, large, heart protruding	0
22	Schindewolf	1900		50	Volvulus, with postoperative death, old mitral endocarditis	Point of maximal impulse 3 fingerbreadths outside nipple	Common cavity on left	0
23	Primrose	1901	M	50 60	Fever, abdominal pain		Foramen on left	0
24	Saver	1902	M		Tuberculous meningitis and peritonitis, old tuberculosis of lung		Common cavity on left	0
25	Plechl	1907	M	60	Pneumonia and pleurisy	Slightly enlarged	Common cavity on left	Pneumonia To left lung
26	Plechl	1907	F	31	Pneumonia		Common cavity on left	Pneumonia 0
27	Verse	1909	F	30	Cyanide poisoning	Normal	Common cavity on left	0
								To left lung
								Only 1 kidney
								Pregnancy, death soon after delivery

Pericardial Defects—Continued

No	Author	Date	Sex	Age	Cause of Death	Cardiac Symptoms and Signs	Size of Pericardium Post Mortem	Type of Pericardial Defect	Pneumonitis	Pleurisy	Adhesions of Heart	Other Anomalies or Conditions
28	Perna	1909	M	68	Chronic enteritis	0	Normal	Common cavity on left	0	0	To left lung	
29	Fabstin	1910	F		Cyanide poisoning	Palpitation after typhoid, but normal physical findings		Common cavity on left			To left lung	
30	Schmincke	1912	M	30	Sepsis	0		Foramen on left				
31	Plaut	1913	M	30	Sepsis	0	Normal	Common cavity on left	0	0	To left lung and wall of chest	
32	Plaut	1913	M	18	Pyogenic meningitis			Common cavity on left	0	0	To left lung and wall of chest	
33	Cameron	1913	M	67	Bronchopneumonia, emphysema, chronic nephritis		Enlarged	Common cavity on left	Bronchopneumonia	0	0	? Traumatic defect
34	McGarry	1914	M	65	Dementia and gastritis	0		Foramen on left, large			0	Several peritoneal anomalies
35	Chase	1916	M	Adult	Tuberculosis of lungs		Normal	Common cavity on left	Tuberculosis		0	Kyphoscoliosis
36	Lang	1921	M		Colitis, hydrothorax, ascites	0	Normal	Common cavity on left	0	Shaggy epicarditis	To left lung	
37	Canavan	1924		56	Dementia paralytica		Very large	Common cavity on left	0	0	0	
38	Monckeberg	1924	M	39				Foramen on left			On all sides	
39	Monckeberg	1924	M	3 wk				Common cavity on left			To left lung	
40	Monckeberg	1924	M	New born				Common cavity on left			To left lung	
41	Grant	1926	M	52	Carcinoma of esophagus, pneumonia			Foramen on left, large, heart protruding	Bronchopneumonia		To left lung, delicate	

42	Breck	1911	M	76	Pneumonia, cardiac insuf ficiency, arterio sclerosis, hypertension	Cardiac insuf ficiency	Enlarged	Common cavity on left	Lobular pneumonia	1,200 cc of clear fluid	Right auricle to perforate dual leaf
43	Watt	1931	M	52	Coronary occlusion	Coronary occlusion	Enlarged	Common cavity on left		0	Long heart with blind apex
44	Chiodini	1932	F	64	Cardioma of cervix, post operative death	Normal heart by physical examination		Foramen on left, large, 2 smaller one on right			To left lung and pericardial rudiment
45	Barsoum	1935	M	35	Cardiac insuf ficiency	? Adherent peri carditis	Giantly enlarged	Common cavity on left		0	0
46	Taft	1869	F	29	Atheromatous mitral stenosis	Dyspnea and anemia, signs of mitral stenosis	II Doubtful Cases	No pericardium, left on right			
47	Jebor	1874						Common cavity on left			Only 2 aortic cusps
48	Meckel	1826	M	Fetus	Gross malfor mation		III Cases in Monsters	Foramen on left, small			Defect in dia phragm
49	Keith	1907		Fetus	Gross malfor mation			Foramen on left			Anomalies of central nervous system
50	Keith	1907		Full term fetus	Anencephaly			Foramen on left, left auricle protruding			Anomalies of central nervous system, abdo men and lungs
51	Ricel	1912	F	New born	Gross malfor mation			Foramen on left, smaller one on right			Defects of cen tral nervous system and in left side of diaphragm
52	Ricel	1912	F	Fetus	Gross malfor mation			Common cavity on left			Anomalies of central nervous system and other anomalies
53	Ricel	1912	M	New born	Gross malfor mation			Foramen on left			No dextrocar dia, anomalies largely on right
54	Robert and Little	1935		15 hr	Multiple abnor malities	? Dextrocardia		Common cavity on left			

Analyzing the data regarding the forty-six cases obtained by including our own case and excluding the two doubtful ones and the seven monsters, we find that with one possible exception (Chiodin's² case) the defect was present only on the left side. Among the seven cases in monsters there was one (Egbert and Little) in which the defect was entirely on the right, and there was one (Risell's first case) in which the defect, like that in Chiodin's case, was thought to be bilateral. Lawson Tait's case, in which no vestige of pericardium was found anywhere, is open to suspicion, both because the description is meager and because the heart, though said to be lying free between the lungs, had no serous surface.

It therefore appears that the defect in nearly every instance is on the left. The type of defect varies from a small foramen connecting the pericardial and the left pleural cavity to one in which there is virtual absence of the left leaf of the parietal pericardium, leaving the heart and the left lung together in a common pleuropericardial cavity.

Moore classified his forty-two cases under three categories: (1) those in which the heart and the lung occupied a common serous cavity (59.5 per cent of the cases), (2) those in which there was only a foramen between the pericardial and the pleural sac (21.4 per cent) and (3) those in which there was either no trace of pericardium or only rudiments thereof (19.1 per cent). It is our feeling that Moore's third type of condition, the existence of which he himself admitted was dubious, was represented entirely by doubtful cases and that the condition has never been conclusively demonstrated. As between the first and the second category we find, as Moore did, about three times as many cases in the former as in the latter. In thirty-four (or 76 per cent) of our forty-six basic cases there was a common serous cavity on the left for both the heart and the left lung, while in eleven (or 24 per cent) there was only a foramen on the left and the heart remained in the pericardial sac. In six cases plus, of course, the seven cases in monsters, there were other congenital anomalies, in addition to the defect of the pericardium. Two affected the heart, one the lungs, one a pleural cavity, one a kidney and one the peritoneum. Since in a number of instances only the heart was carefully described, it may well be that other defects were overlooked.

Thirty-three of our basic cases (77 per cent) occurred in males, as against ten in females. This is in agreement with the finding of Maude Abbott, who listed seventeen males and six females. The age at the time of death varied from birth to 75 years, with a mean of 41.6 years. In comparison the mean age at death for the United States area of

² Chiodin was frank enough to admit that the smaller defect present on the right may have been an artefact produced at autopsy.

registration for 1900 was 35.1 years³ The discrepancy between these figures is probably due to the fact that in our series only 5.3 per cent of the cases represent infant mortality, while in the census report deaths of infants under 1 year of age made up 20.8 per cent of the total If, therefore, deaths of infants under 1 year of age are excluded from both series, the mean age at death in our series of cases of pericardial defects becomes 43.9 years, while that for the registration area becomes 44.2 years

These figures indicate that the anomaly has no appreciable influence on life expectancy In only one instance (Boxall) was death apparently due directly to the defect The case was that of a woman of 28 who three days post partum died suddenly, with symptoms suggestive of pulmonary embolism Autopsy disclosed that the whole heart had herniated through a large foramen in the left leaf of the pericardium and had become partially strangulated It was suggested that changes in intrathoracic pressures following delivery were responsible for this mishap In fifteen cases the absence of cardiac symptoms was commented on, while in only three were circulatory symptoms recorded that were not obviously due to associated disease, such as hypertension or coronary thrombosis In two of these cases (those of Wolf and Ebstein) there was mild angina, and in one case the symptoms occurred after typhoid In the third case it was believed during life that there was adherent pericarditis, death was due to cardiac insufficiency the cause of which was not explained

In twenty-three instances the size of the heart was described In four of the fourteen hearts said to be enlarged the enlargement was presumably due to associated cardiovascular diseases (coronary sclerosis, hypertension, chronic nephritis and mitral endocarditis) This leaves nineteen cases, in nine cases the heart was of normal size, which agrees with the observations of Grant that in only 50 per cent of the cases was the heart enlarged

Although it thus appears that a pericardial defect is rarely the direct cause of death or of cardiac symptoms and that it does not necessarily cause cardiac enlargement, it may yet be detrimental to health by exposing the heart to pulmonary infection This has been recognized previously by Abbott and by White, and the case cited is a conspicuous example How serious a menace this may be is shown by the fact that in nine (19 per cent) of the cases listed in our series death was due to pneumonia while in twelve (27 per cent) there was fresh pleuropericarditis of some kind In six instances (cases reported by Bristowe, Pisek, Adersen, Picchi [case 1], Beck and ourselves)

³ Mortality Statistics, 1900-1904, Special Reports, United States Department of Commerce and Labor, Bureau of Census, 1906, p. 22

pleuropericarditis was associated with pneumonia, while in three others (cases reported by Lang, Chiari [case 2] and Weisbach) its origin was not clear. In all nine, save perhaps in Adersen's case, in which there was also a ruptured spleen, it was responsible for death. In two cases (those of Baly and Powell) pleuropericarditis was associated with pulmonary tuberculosis, and in Orth's case an aortic aneurysm produced a massive hemopericardiothorax by rupturing into the pericardium. Further evidence of former, albeit localized and transient, pleuropericardial infections is found in the fact that in twenty-five (74 per cent) of the thirty-four cases in which the serous surfaces were adequately described, there were adhesions between the epicardium and the left lung, the diaphragm or the pericardial remnant. In one instance (Perna) these adhesions were studied histologically and, as expected, showed evidence of old inflammation. It may be deduced that the presence of these adhesions shows that pleuropericardial infection is by no means always fatal, at least they indicate that it is common. No correlation could be made out between the size of the heart and the presence or absence of adhesions.

DIAGNOSIS

The clinical diagnosis of congenital defect of the pericardium has never been made during life. Maude Abbott has stated, however, that this need not be impossible and should be based on (1) the greatly increased mobility of the heart (2) its occasional hypertrophy without clinical cause and (3) its frequent displacement to the left. In our patient the mobility was not adequately tested, owing to the patient's extreme illness, and was probably impaired anyway by the adhesions and the plastic exudate, but the cardiac pulsations under the fluoroscope were conspicuous. Cardiac enlargement was not present, in spite of the presence of adhesions. The unexplained displacement of the heart to the left without deviation of the trachea was the source of much clinical comment. Thus our case bears out at least one of Abbott's diagnostic criteria. The hypothecation of these criteria is, of course, partly presumptive. Clinical data on increased cardiac mobility are entirely lacking, though the approximately 50 per cent incidence of cardiac enlargement is definite. The incidence of displacement is also rather uncertain. In the 24 per cent of cases in which there was only a pleuropericardial foramen on the left, the heart was in normal position. Of the 76 per cent of cases in which there was a common pleuropericardial cavity on the left, ours is the first in which an adequate antemortem description of the cardiac position has been given. For the others since the anatomic description was given only after the anterior thoracic wall had been removed and the left lung had been collapsed through the opening of the left pleura, the data were rather uncertain as to the

cardiac position But it seems logical, as Maude Abbott has maintained, that the complete absence of the left leaf of the parietal pericardium should cause some luxation of the heart to the left We therefore feel that, although the diagnosis is probably impossible in cases in which the defect is represented only by a foramen, in those in which there is a common cavity on the left the diagnosis may be suspected from (1) unexplained displacement of the heart to the left and further confirmed if, in the absence of adhesions, there is (2) abnormal mobility of the heart Unexplained cardiac enlargement (3), if present, would be further evidence in favor of the diagnosis, though its absence would not be significant

SUMMARY

A description is given of a patient showing congenital absence of the left leaf of the parietal pericardium, with an interpleural window in the upper portion of the anterior mediastinum

This is the first case reported in the literature in which adequate clinical data have been given and in which fluoroscopic examination has been included

In a survey of the literature forty-five definite instances of this defect have been found, together with seven other instances in monstrous births and two doubtful cases

Analysis of these cases reveals that the defect was almost invariably on the left, that in 76 per cent of the cases it was so complete on that side that the heart and the left lung were in a common serous cavity, that in 77 per cent of the cases the subject was a male, and that the condition is not incompatible with normal life, having in only one instance been directly responsible for death and having otherwise possibly caused cardiac symptoms in only three cases

Unexplained cardiac enlargement may occur (in about half the cases), but it is apparently not related to the presence or absence of adhesions

The chief danger from the defect lies in exposing the heart to pulmonary infection, with death in 27 per cent of the cases, including our own, associated with pleuropericarditis

Although in no case as yet has the condition been diagnosed ante mortem, this should be possible in some instances, on the basis of certain criteria adapted from Maude Abbott

NOTE—Since the writing of this article an interesting report has appeared by E Dahl (*Med rev*, Bergen 54: 312 [July] 1937) of a man aged 28 with bilateral exudative pulmonary tuberculosis in whom pneumopericardium appeared and persisted after artificial pneumothorax was induced through the left axilla The author stated the opinion that this was a case of congenital defect but could not prove it was not due to the disease or to trauma The diagnostic interest is obvious

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FOUR LEAD ELECTROCARDIOGRAM IN CASES OF RECENT CORONARY OCCLUSION

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The value of electrocardiograms in cases of recent coronary occlusion has been definitely established. The added value of records obtained from leads with one electrode placed on the chest has recently come into prominence. Sufficient information has been published¹ to establish a fair basis for their interpretation, and obscure points are rapidly being clarified.

Accumulated evidence has indicated that the chest lead is often of definite assistance in determining the presence, the location and to some degree the age of myocardial infarcts. The published reports of a number of cases in which autopsies were performed furnish additional evidence of the accuracy of these electrocardiographic interpreta-

From the Heart Station, Michael Reese Hospital

Aided by the A. D. Nast Fund for Cardiac Study

1 (a) Wolferth, C. C., and Wood, F. C. Electrocardiographic Diagnosis of Coronary Occlusion by Use of Chest Leads, *Am J M Sc* **183** 30, 1932, (b) Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, *M Clin North America* **16** 161, 1932. (c) Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C. Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch Int Med* **52** 752 (Nov.) 1933. (d) Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klosternmeyer, L. L. The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* **16** 155, 1933. (e) Hoffman, A. M., and Delong, E. Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Disease, *Arch Int Med* **51** 947 (June) 1933. (f) Levine, Louis. Chest Leads in Coronary Occlusion, *M J & Rec* **136** 421, 1932. (g) Goldbloom, A. A. Clinical Evaluation of Lead IV (Chest Leads), *Am J M Sc* **187** 489, 1934. (h) Bohning, A., and Katz, L. N. The Four Lead Electrocardiogram in Coronary Sclerosis, *ibid* **189** 833, 1935. (i) Katz, L. N., and Kissin, M. A Study of Lead IV, *Am Heart J* **8** 595, 1933. (j) Liberson, A., and Liberson, F. The Value of Posterior-Anterior Chest Leads in Cardiac Diagnosis, *Ann Int Med* **6** 1315, 1933. (k) Master, Arthur M. The Precordial Lead in One Hundred and Four Normal Adults, *Am Heart J* **9** 511, 1934. (l) Shipley, R. A., and Halloran, W. R. Four Lead Electrocardiogram in Two Hundred Normal Men and Women, *ibid* **11** 325, 1936. (m) Roth, Irving R. On the Use of Chest Leads in Clinical Electrocardiography, *ibid* **10** 798, 1935.

tations, but the significance of some details is still in controversy. Thus, some authors have stressed the contour of the T wave,² others, the contour and direction of the QRS complex³ and still others, the appearance of the deviation in the ST segment.⁴ In the greater number of instances the abnormalities in the precordial leads are in accord with those in the conventional three leads, but this is not true of all cases. The reason for this has not as yet been clearly established. There are a number of instances in which the chest lead is characteristic of infarction, but the conventional leads show none of the classic changes.⁵ In a smaller group the conventional three leads may show the characteristic type of change, but the chest lead may be atypical.⁶ It is therefore not surprising that there is some feeling of uncertainty in regard to the interpretation of chest leads. In the hope that we might be able to clarify some of this confusion, we have made a careful study of the four lead electrocardiogram with a large group of patients.

PLAN OF THE STUDY

(a) *Selection of Cases*—The records of 200 consecutive patients from the charity wards, private pavilion and clinics of Michael Reese Hospital were studied. These patients had been referred for electrocardiograms during years 1934, 1935 and 1936. The selection was made on the basis of abnormalities in four lead

2 Wood, F. C., and Wolferth, C. C. Huge T-Waves in Precordial Leads in Cardiac Infarction, *Am Heart J* **9** 706, 1934.

3 (a) Johnston, F. D., Hill, I. G. W., and Wilson, F. N. The Form of the Electrocardiogram in Experimental Myocardial Infarction. II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *Am Heart J* **10** 889, 1935. (b) Wilson, F. N., Hill, I. G. W., and Johnston, F. D. The Form of the Electrocardiogram in Experimental Myocardial Infarction. III. The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *ibid* **10** 903, 1935. (c) Wilson, F. N., Johnston, F. D., and Hill, I. G. W. The Form of the Electrocardiogram in Experimental Myocardial Infarction. IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *ibid* **10** 1025, 1935. Wilson and others.^{1a}

4 (a) Wood, F. C., and Wolferth, C. C. An Electrocardiographic Study of Experimental Coronary Occlusion. The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Current, *J Clin Investigation* **11** 815, 1932. (b) Wolferth, C. C., Wood, F. C., and Bellet, S. Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle. Electrocardiographic Characteristics, *Arch Int Med* **56** 77 (July) 1935. (c) Wood, F. C., and Wolferth, C. C. Experimental Coronary Occlusion, *ibid* **51** 771 (May) 1933. (d) Bellet, S., and Johnston, C. G. The Effect of Coronary Occlusion upon the Initial Phase of the Ventricular Complex in Precordial Leads, *J Clin Investigation* **13** 725, 1934.

5 Wolferth and Wood.^{1a} Katz and Kissin.¹¹ Wood and Wolferth.^{4a}

6 Wolferth and Wood.^{1b} Katz and Kissin.¹¹

electrocardiograms which were indicative of *recent* myocardial infarction. Cases in which no diagnostic electrocardiographic features were revealed in the initial or serial curves were rejected regardless of the clinical picture. Many of the records were obtained within a few hours after the clinical attack, and a second record was often obtained within from twenty-four to forty-eight hours. These were followed in many instances by curves obtained every three or four days during the first two weeks and then every week or every fortnight during the rest of the patient's stay in the hospital. After leaving the hospital many patients returned every few months for follow-up study.

TABLE 1—*Sex and Age Incidence in Present Series of Two Hundred Cases of Myocardial Infarction*

	Total Cases, Percentage	Known Dead (66%), Percentage	Autopsies (25%), Percentage
Men	76	75.7	88
Women	24	24.3	12
Age at time of attack			
Under 30 years	0.5	0.0	0
30 to 39 years	5.0	4.5	0
40 to 49 years	21.0	15.0	20
50 to 59 years	38.5	30.5	28
60 to 69 years	29.5	42.5	44
70 to 79 years	5.0	6.0	4
80 years or more	0.5	1.5	4

TABLE 2—*Incidence of Mortality in the Two Hundred Consecutive Cases of Coronary Occlusion*

	Type of Infarction			All Types
	Anterior	Posterior	Combined	
Total number of cases	119	73	8	200
Fate unknown, %	25.0	29.0	12.5	26.0
Known to be alive, %	38.0	48.0	25.0	41.0
Known to be dead, %	37.0	23.0	62.5	33.0
Died in hospital, %	25.0	15.0	50.0	22.5
Autopsy obtained, %	12.5*	2.5	37.5	10.0

* Two cases of coronary sclerosis without infarction.

Six hundred and fifty records were thus obtained. In 44 cases only one record was made, usually because death occurred before a second could be obtained. In the remaining 156 cases the average number of records was four, the least number being two and the greatest twenty. In 32 cases the curves covered only the first week of illness, and in 33 only the stay in the hospital, in the other 91 cases there were follow-up records. Autopsies were obtained in 20 of the 200 cases. In 5 other cases not in the original series autopsy was performed while this report was being prepared. Our report therefore includes 25 cases of proved recent myocardial infarction in which four lead electrocardiograms were made (table 3 and figs 1 to 7, inclusive). For comparison we have added 2 cases of recent multiple small infarcts and 8 cases of moderately advanced coronary sclerosis without infarcts in all of which autopsy was performed (table 3 and figs 8 to 10, inclusive).

(b) *Criteria Used in Analyzing the Records*—The changes observed in our 25 cases in which autopsy was performed were correlated with the electrocardio-

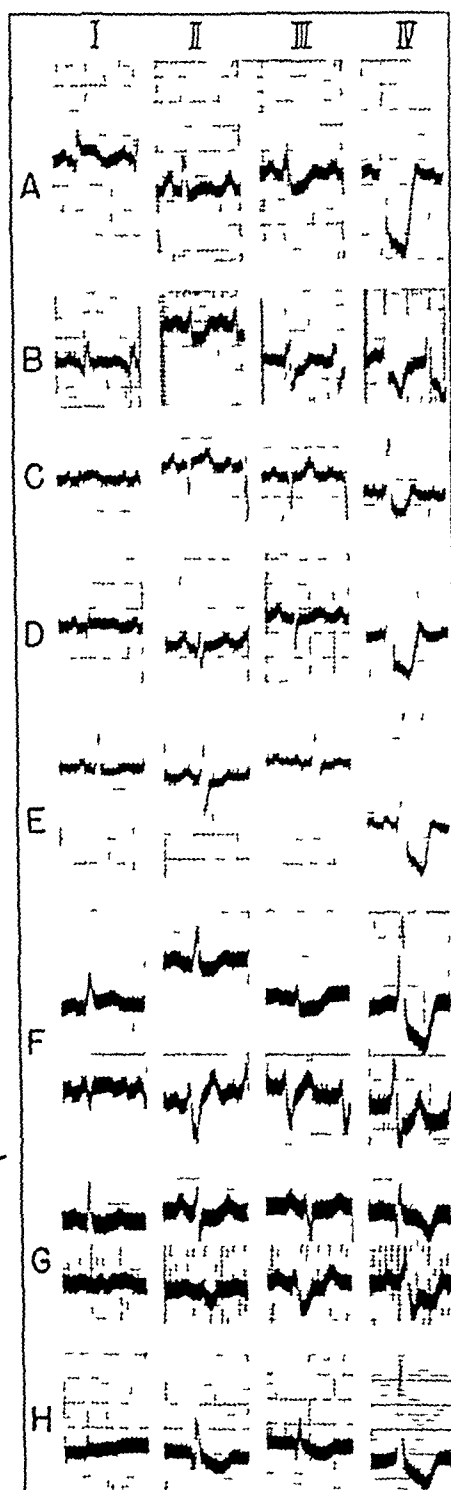


Fig 1—Electrocardiograms of 8 patients (cases A to H) with proved uncomplicated infarction of the anterior wall due to a suddenly occurring thrombus in the left anterior descending coronary artery. The necropsy reports are summarized in table 3.

Case A		Case B		Case C		Case D	
Attack	8/20/35	Attack	4/ 1/35	Attack	5/15/35	Attack	6/18/35
Curve taken	8/20/35	Curve taken	3/ 1/35	Curve taken	5/23/35	Curve taken	6/22/35
Death	5/21/35	Death	4/ 5/35	Death	6/10/35	Death	7/ 9/35
Case E		Case F		Case G		Case H	
Attack	7/20/35	Attack	2/24/35	Curve taken	7/ 8/35	Attack	12/16/32
Curve taken	5/23/35	Curves taken	2/24/35	before attack	7/ 8/35	Curve taken	12/16/32
Death	5/23/35	Death	2/27/35	Attack	6/19/35	Death	12/22/32
				Curve taken	6/22/35		
				Death	6/24/35		

TABLE 4—Analysis of Abnormalities in Standard Three Leads

Types of Infarction												
	Anterior			Posterior			Combined			All Types		
	Series A Consecu- tive Cases	Series B Known Fatal Cases	Series C Autop- sies	Series A Consecu- tive Cases	Series B Known Fatal Cases	Series C Autop- sies	Series A Consecu- tive Cases	Series B Known Fatal Cases	Series C Autop- sies	Series A Consecu- tive Cases	Series B Known Fatal Cases	Series C Autop- sies
Number of cases in series	119	44	15	73	17	4	8	5	6	200	66	23
Percentage of cases in series	59.5	66.7	60.0	36.5	23.7	16.0	4.0	7.6	24.0	100.0	100.0	100.0
Frequency of Abnormality, Percentage												
Changes in rhythm	3.4	9.1	6.7	4.1	0.0	0.0	12.5	0.0	0.0	4.0	6.0	4.0
Extrasystoles	5.9	5.0	20.0	2.7	11.8	0.0	0.0	0.0	0.0	4.5	12.1	12.0
Auricular fibrillation	6.7	13.6	26.7	2.7	11.8	50.0	25.0	20.0	66.7	6.0	13.6	40.0
QRS deviations	13.4	18.2	66.7	1.4	0.0	0.0	25.0	0.0	33.3	9.3	12.1	48.0
Intraventricular block	99.2	100.0	100.0	98.6	100.0	100.0	100.0	100.0	100.0	99.0	100.0	100.0
Low "voltage"	37.8	45.5	33.3	41.1	52.9	25.0	100.0	20.0	66.7	41.5	51.5	40.0
Notching	16.8	29.5	26.7	15.1	23.5	0.0	25.0	20.0	33.3	16.5	27.3	24.0
Left axis shift	22.7	25.0	33.3	50.7	47.0	25.0	25.0	40.0	33.3	33.0	31.8	32.0
Left ventricular preponderance	4.2	6.8	6.7	0.0	0.0	0.0	0.0	0.0	0.0	2.5	4.6	4.0
Right axis shift												
ST deviations												
Negative ST ₁	38.6	47.7	40.0	68.5	94.1	100.0	75.0	80.0	66.7	51.0	62.1	56.0
Negative ST ₂	47.6	61.4	66.7	39.7	17.6	50.0	25.0	20.0	33.3	45.5	46.9	56.0
Negative ST ₃	26.9	38.6	55.3	6.8	0.0	0.0	12.5	20.0	0.0	19.0	27.3	32.0
Positive ST ₁	16.8	25.0	40.0	5.5	0.0	0.0	0.0	0.0	0.0	12.0	16.6	24.0
Positive ST ₂	18.5	13.6	13.3	35.6	58.8	25.0	12.5	20.0	16.7	24.5	27.7	16.0
Positive ST ₃	25.2	15.9	20.0	63.0	88.2	100.0	75.0	60.0	33.3	41.0	37.8	36.0
T deviations												
Negative T ₁	63.9	65.9	33.3	1.4	0.0	0.0	25.0	40.0	50.0	39.5	46.9	32.0
Negative T ₂	37.0	27.3	13.3	49.3	64.7	50.0	62.5	60.0	33.3	42.5	39.3	24.0
Negative T ₃	9.2	18.2	13.3	78.1	82.3	100.0	37.5	20.0	50.0	38.5	34.8	36.0
Convex ST ₁	20.2	27.3	40.0	0.0	0.0	0.0	0.0	0.0	0.0	12.0	18.1	24.0
Convex ST ₂	0.8	2.3	0.0	11.0	17.6	0.0	0.0	0.0	0.0	4.5	6.0	0.0
Convex ST ₃	0.0	0.0	0.0	49.3	70.6	75.0	25.0	20.0	16.7	19.0	19.7	16.0
Biphasic T ₁	5.9	9.1	13.3	13.1	17.6	25.0	25.0	20.0	33.3	10.0	12.1	20.0
Biphasic T ₂	8.4	15.9	20.0	11.0	5.9	25.0	0.0	0.0	0.0	9.0	12.1	16.0
Biphasic T ₃	1.7	2.3	6.7	1.4	0.0	0.0	25.0	20.0	0.0	2.5	3.0	0.0

TABLE 5—Analysis of Deviations in Lead IV

	Types of Infarction											
	Anterior				Posterior				Combined			
	Series A				Series B				Series A			
	Consecu- tive Cases	Known Fatal Cases	Series B Autop- sies	Series C	Consecu- tive Cases	Known Fatal Cases	Series B Autop- sies	Series C	Consecu- tive Cases	Known Fatal Cases	Series A Autop- sies	Series B Autop- sies
Number of cases in series	119	41	15	73	17	73	1	8	5	5	0	25
	Frequency of Abnormality, Percentage											
P _t	36.2	36.8	66.7	34.3	23.5	20.6	0.0	75.0	80.0	83.3	13.0	70.0
Diphase	16.8	18.2	13.3	20.6	20.1	15.0	0.0	25.0	20.0	0.0	18.5	21.2
Iso electric	21.9	22.7	20.0	15.0	23.6	23.6	0.0	0.0	0.0	0.0	18.5	21.2
Negative	15.1	2.3	0.0	30.1	23.5	23.5	25.0	0.0	0.0	0.0	20.0	7.6
Q _t *	1.8	6.6	80.0	0.8	0.0	80.8	76.1	0.0	0.0	0.0	31.5	12.1
Deep	11.8	9.0	0.0	0.0	0.0	0.0	75.0	50.0	10.0	10.0	38.5	28.8
QRS,t	19.6	61.1	73.3	5.5	0.0	6.8	0.0	0.0	0.0	0.0	31.5	11.0
Monophasic upright	26.1	27.3	20.0	72.6	88.2	72.6	75.0	50.0	60.0	83.3	20.0	21.2
Mainly positive	19.3	9.0	6.7	1.1	0.0	1.1	0.0	0.0	0.0	0.0	10.0	31.8
Diphase 1st phase down	1.2	2.3	0.0	13.7	5.9	13.7	0.0	0.0	0.0	0.0	3.0	1.5
Diphase 1st phase up	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.5	1.5
Mainly down	5.1	1.5	0.0	58.9	82.3	41.1	50.0	37.5	10.0	0.0	26.0	27.3
ST _t	10.9	1.5	0.0	1.1	11.8	30.2	0.0	12.5	0.0	0.0	8.5	6.0
Positive	41.5	41.0	13.3	30.2	0.0	6.8	25.0	50.0	40.0	50.0	39.5	30.1
Iso electric	39.5	50.0	86.7	6.8	5.9	6.8	25.0	0.0	20.0	33.3	26.0	36.3
Negative, —2 mm or less	13.7	25.0	6.7	4.1	3.9	5.5	0.0	25.0	20.0	0.0	28.5	19.7
Negative, more than —2 mm	33.6	41.0	33.3	5.5	0.0	63.0	75.0	12.5	20.0	33.3	22.5	28.8
T _t	18.5	25.0	53.3	63.0	41.1	27.1	25.0	62.5	60.0	33.3	36.0	31.8
Positive	4.2	9.0	6.7	27.1	53.0	0.0	25.0	0.0	0.0	33.3	13.0	19.7
Diphase												
Negative, less than —8 mm												
Negative, —8 mm or more												

* Primary negative deflection

† Main deflection

TABLE 6—Classification of Types of Coronary Insufficiency

I Subacute	Type of Myocardial Involvement		Type of Coronary Involvement	Location of Myocardial Involvement	Most Common Type of Electrocardiographic Change	Cases Illustrating the Type
	Definite myocardial infarction	A Uncomplicated or classic forms				
II Chronic, progressive or nonprogressive	Fibrosis without infarction	B Complicated or atypical forms	Thrombotic occlusion	Anterior infarction	ST ₁ + T ₁ — QRS ₁ + ST ₁ — T ₁ + or ±	8 cases (chart 1)
				Posterior infarction	ST ₁ + T ₁ — QRS ₁ ± ST ₁ + T ₁ —	3 cases (charts 1A to C)
			Sclerotic occlusion	Anterior infarction	ST ₁ — T ₁ — QRS ₁ + T ₁ ±	7 cases (charts 2 and 3)
			Both arteries occluded	Posterior infarction	T ₃ — QRS ₁ + or ±	1 case (chart 4D)
III Acute, transitory	Transitory ischemia			Old posterior with recent anterior infarction	Often like anterior infarction	1 cases (charts 5, 7A and B and 11A)
				Old anterior with recent posterior infarction	Often like posterior infarction	4 cases (charts 6A and B, 7C and 11B)
			No complete occlusion	Multiple small infarcts	Atypical	2 cases (chart 8A and B)
II Chronic, progressive or nonprogressive	Fibrosis without infarction		Advanced coronary sclerosis	No infarct visible, fibrosis usual	1 Like anterior infarction 2 Like posterior infarction 3 Indeterminate	2 cases (chart 10A and B) 5 cases (chart 9)
			Indeterminate	Indeterminate	ST and T deviations variable	2 cases (charts 8C and 10C)

graphic changes in cases reported in the literature with autopsy data.⁷ In this manner the electrocardiographic criteria for the following two groups were established (1) recent anterior type of infarct, and (2) recent posterior type of infarct. These criteria are based, therefore, on the study of the electrocardiograms in a total of 239 cases in which the diagnosis was verified at autopsy. In the greater number of cases reported in the literature only the conventional three leads were recorded, but in our own cases and a limited number of the others four lead records were made. (More exact details of the electrocardiographic criteria derived by us can be seen in table 6, which will be discussed later.) The greater

7 (a) Herrick, J. B. Thrombosis of the Coronary Arteries, *J. A. M. A.* **72** 387 (Feb 8) 1919. (b) Smith, F. M. Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch. Int. Med.* **32** 497 (Oct.) 1923. (c) Kahn, M. H. The Electrocardiographic Signs of Coronary Thrombosis and Aneurysm of the Left Ventricle of the Heart, Boston M. & S. J. **187**:788, 1922. (d) Clarke, N. E., and Smith, F. J. The Electrocardiogram in Coronary Thrombosis, *J. Lab. & Clin. Med.* **11** 1071, 1925. (e) Pardee, H. E. B. Heart Disease and Abnormal Electrocardiograms, with Special Reference to Coronary T-Wave, *Am. J. M. Sc.* **169** 270, 1925. (f) Barnes, A. R. The Electrocardiographic Localization of Myocardial Infarcts, *M. Clin. North America* **14** 671, 1930. (g) Q and T Types of Electrocardiograms. Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, *Am. Heart J.* **9** 722, 1934. (h) Barnes, A. R., and Whitten, M. B. Study of the R-T Interval in Myocardial Infarction, *ibid.* **5** 142, 1929. (i) Willius, F. A., and Barnes, A. R. Myocardial Infarction. An Electrocardiographic Study, *J. Lab. & Clin. Med.* **10** 427, 1925. (j) Barnes, A. R. Correlation of Initial Deflections of Ventricular Complex with Situation of Acute Myocardial Infarction, *Am. Heart J.* **9** 728, 1934. (k) Parkinson, John, and Bedford, D. E. Successive Changes in the Electrocardiogram After Cardiac Infarction, *Heart* **14** 195, 1928. (l) Levine, Samuel A., and Brown, C. L. Coronary Thrombosis. Its Various Clinical Features, *Medicine* **8** 245, 1929. (m) Stewart, H. J. The Relation of Clinical, Including Electrocardiographic, Phenomena to Occlusion of the Coronary Arteries Based on the Observation of a Case, *Am. Heart J.* **4** 393, 1929. (n) Gilchrist, A. R., and Ritchie, W. T. The Ventricular Complexes in Myocardial Infarction and Fibrosis, *Quart. J. Med.* **23** 273, 1930. (o) Nathanson, M. D. Electrocardiogram in Coronary Disease, *Am. Heart J.* **5** 257, 1930. (p) Cooksey, W. D., and Freund, H. A. Serial Electrocardiographic Studies in Coronary Thrombosis, *ibid.* **6** 608, 1931. (q) Fenichel, N., and Kugell, V. The Large Q-Wave of the Electrocardiogram. A Correlation with Pathological Observations, *ibid.* **7** 235, 1932. (r) Winternitz, M. The Initial Complex of the Electrocardiogram After Infarction of the Human Heart, *ibid.* **9** 616, 1934. (s) France, R. The Large Q-Wave in Lead III of the Electrocardiogram, *Am. J. M. Sc.* **187** 16, 1934. (t) White, Paul D. Electrocardiographic Evidence of Recent Coronary Thrombosis Superimposed on Bundle-Branch Block Resulting from Previous Coronary Disease, *Am. Heart J.* **10** 260, 1934. (u) Appelbaum, E., and Nicolson, G. H. B. Occlusive Disease of the Coronary Arteries, *ibid.* **10** 662, 1935. (v) Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N. Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *ibid.* **10** 567, 1935. (w) Jervell, Anton. Elektrokardiographische Befunde bei Herzinfarkt, *Acta med. Scandinav.*, supp 68, 1935, p. 1. Wilson and others.^{1a} Hoffman and Delong.^{1b} Wolferth, Wood and Bellet.^{4b}

number of the 200 cases of our series were therefore fitted into one of these two groups according to the evidence afforded by the four lead electrocardiograms. A small number of cases were placed in a group designated as instances of combined anterior and posterior infarcts (one of the infarcts being recent). The basis for this third classification was either autopsy evidence of a combination of infarcts or, when autopsy was not performed, conclusive evidence in serial records of sudden coronary closure on two or more distinct occasions, with infarction in two regions.

(c) *Method of Analysis*—The frequency of the various abnormalities in each of the four leads was determined for the foregoing groups. For purposes of comparison the cases were divided into three series: series A, consisting of the entire 200 consecutive cases; series B, consisting of the cases in which death was known to have occurred; and series C, consisting of the cases in which the diagnosis was verified at autopsy.

THE MANNER IN WHICH THE CHEST LEADS WERE TAKEN

There is still considerable confusion concerning the manner in which the chest lead should be taken, as regards (1) the size of the chest electrode, (2) the placement of the chest and distant electrodes, (3) the manner of connecting the electrodes to the galvanometer and (4) the manner of designating the lead.

Fortunately, many of these points have been clarified by experience. Thus it is almost universally agreed that the right arm terminal should be connected to the chest electrode and the left leg terminal to the distant electrode, a method which we have used consistently and which we urge as a universal practice. There is no logical reason for making the reverse connection, recently urged, since the connections are purely a matter of convention.

Although Wolferth and Wood¹² originally placed the distant electrode on the posterior part of the chest, they found that the variations in the contour of the chest lead are but little affected by a change in position of the distant electrode, so long as this is not brought too close to the heart. This is confirmed by our own experience and that of others. The electrode nearest the heart dominates the curve. For convenience we have used the left leg electrode as the distant electrode in our work. We see no theoretical advantage and some practical disadvantages in the use of the special distant electrode suggested by Wilson and his colleagues.⁸

The location of the chest electrode is of considerable importance. A small shift in its position will alter the record considerably. Hence,

⁸ Wilson, F. N., Johnston, F. D., and Hill, I. G. W. The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant from the Heart and the Other Near or in Contact with the Ventricular Surface. I. Observations on the Cold Blooded Heart, *Am Heart J* **10** 163, 1934, II. Observations on the Mammalian Heart, *ibid* **10** 176, 1934.

a fixed position with respect to some bony structure seems desirable to insure consistency when successive records are taken. We have not found it satisfactory to place the chest electrode over the apex of the heart, as is done in some clinics. The apex is not a fixed point in relation to the chest or to the parts of the heart. It may alter its location considerably from time to time even in the same patient and it cannot always be accurately determined. The variability in these factors makes

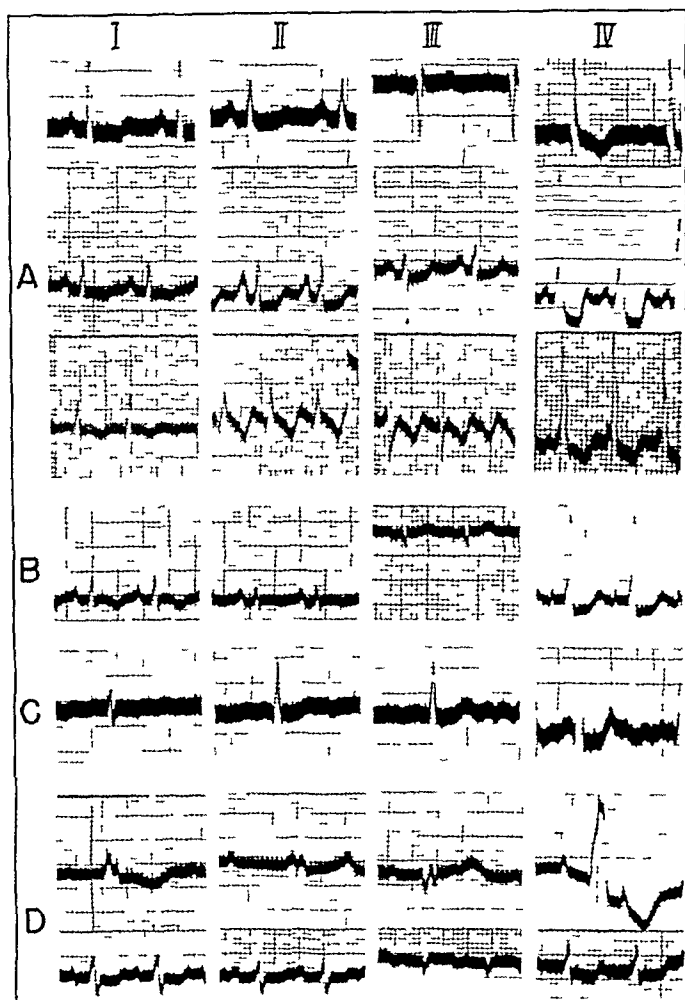


Fig 2—Electrocardiograms of 4 patients (cases A to D) with proved infarction of the anterior wall due to slowly occluding or narrowing sclerotic plaques in the left anterior descending coronary artery associated with sclerotic changes in the right coronary artery. The necropsy reports are summarized in table 3.

Case A	Case B	Case C	Case D
Curve taken before attack 10/25/35	Attack 4/25/33	Attack 11/ 1/34	Attack 8/27/32
Attack 12/15/35	Curve taken 5/31/33	Curve taken 12/21/34	Curves taken 9/ 1/ 2
Curves taken 12/18/35	Death 6/ 2/33	Death 1/16/35	9/12/ 2
12/26/35			Death 9/16/ 2
Death 12/31/35			

this type of chest lead occasionally confusing. After considerable experimentation we have found that for the vast majority of patients the most favorable application of the chest electrode is just to the left

of the sternal margin in the fourth intercostal space. This single chest contact is in our experience by far the most informative. Chest leads taken in this manner are fairly uniform for normal adults. In cases of coronary disease this chest lead is particularly useful, since it depicts the events in an area of the heart which is sometimes not recorded in the conventional three leads. This site on the chest is free from intervening lung and has three sides marked by bony structures. We have investigated various sites on the chest in many of our cases and have found that only occasionally in instances of posterior infarction will changes be detectable with the electrode in the left anterior axillary line and not demonstrable with the electrode in the left parasternal position.

Within reasonable limits the size of the chest electrode makes little difference. For technical simplicity we have used the same electrodes for the chest as those employed for the extremities ($1\frac{1}{2}$ by $2\frac{1}{2}$ inches [3.8 by 6.4 cm]).

A great deal of confusion at present exists because of differences in nomenclature. We believe it will simplify matters if the term lead IV is restricted to a lead connecting the chest with a distant electrode. This should be amplified by describing the location of the chest electrode. Thus, we describe our lead IV as follows: lead IV (fourth interspace, left parasternal line—left leg).

RESULTS

(a) *Incidence and Mortality*—In our series there were over three times as many men as women (table 1). This greater frequency in men is in accord with the findings reported by others.⁹ The mortality rate was about the same for each sex.

The average age at which the attacks occurred was 55 years for our entire series of patients and but little more for those that died (57 years). The scatter of the age incidence was wide (table 1), but the greater number of attacks occurred in the fifth decade. This is also in close agreement with the findings of others.¹⁰ Death occurred more often in the sixth decade.

9 (a) Levy, H., and Boas, E. P. Coronary Artery Disease in Women, *J. A. M. A.* **107** 97 (July 11) 1936. (b) Conner, Lewis A., and Holt, E. The Subsequent Course and Prognosis in Coronary Thrombosis, *Am. Heart J.* **5** 705, 1930. (c) Polanco, Mario. The Relation of Coronary Sclerosis to Symptoms and Its Distribution in Two Hundred and Forty-Two Fatal Cases, *Am. J. M. Sc.* **192** 840, 1936. (d) Levine and Brown.⁷¹

10 (a) Barnes, A. R., and Ball, R. G. The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* **183** 215, 1932. (b) Mullins, W. L. Age Incidence and Mortality in Coronary Occlusion, *Pennsylvania M. J.* **39** 322, 1936. (c) Levine and Brown.⁷¹ Appelbaum and Nicolson.⁷⁴ Conner and Holt.^{9b} Polanco.^{9c}

The data pertaining to mortality have been assembled in table 2. It is significant that the known mortality is highest in cases of combined anterior and posterior infarctions, since it has already been established that death is more frequent after a second or third closure.¹¹ The mortality is higher during the first few weeks after the attack than later. Delayed death was frequently associated with another attack.

(b) *Detailed Report of the Cases in Which Recent Infarction Was Shown at Autopsy*—There have been so few reports of cases of recent infarction in which the diagnosis was verified at autopsy and in which

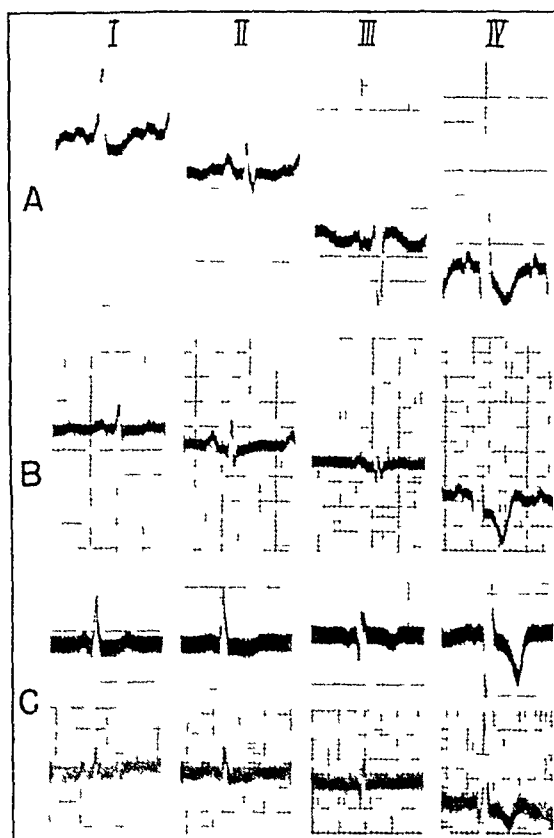


Fig. 3—Electrocardiograms of 3 patients (cases A to C) with proved infarction of the anterior wall due to slowly occluding or narrowing sclerotic plaques in the left anterior descending coronary artery associated with sclerotic changes in the right coronary artery. The necropsy reports are summarized in table 3.

Case A		Case B		Case C	
Attack	12/30/34	Attack	2/21/36	Curve taken before attack	5/7/36
Curve taken	1/3/35	Curve taken	2/25/36	Attack	5/29/36
Death	1/22/35	Death	3/8/36	Curve taken	5/31/36
				Death	5/31/36

four lead electrocardiograms were made that the details of these 25 cases are placed on record. The necropsy data based on the report of

11 (a) Master, A. M., Jaffe, H. L., and Dack, S. Multiple Attacks of Coronary Artery Thrombosis. *Am Heart J* 12: 244 (Aug.) 1936. (b) Wilson and others.¹⁰ Goldbloom.¹²

D1 O Saphir, of the department of pathology, were analyzed and are shown in table 3, and the electrocardiographic records are shown in figures 1 to 7. These 25 cases include 15 cases of recent anterior infarction (figs 1 to 3), 4 cases of recent posterior infarction (fig 4) and 6 cases of combined anterior and posterior infarctions, one of the infarcts being recent (figs 5 to 7).

(c) *Frequency of Types*—As table 4 shows, recent anterior infarction occurred more often than either of the other two types, both in the entire series of 200 cases and in the 25 cases in which autopsy was performed. The greater incidence of the anterior type is in accord with that shown in other reports.¹² This study shows further that infarcts are more correctly localized when all four leads are analyzed than when the analysis is confined to conventional leads, since the incidence of anterior and of posterior infarct based on four lead electrocardiograms corresponds much more closely with postmortem reports than the incidence based on three lead electrocardiograms. The smaller number of recent posterior infarcts in the series of cases in which autopsy was performed as compared with the greater number of this type in the entire series is in accord with the prevailing opinion that for posterior infarcts the mortality rate is lower than for anterior infarcts.

The combined infarction was the least common variety, but in the series of cases in which autopsy was performed it was six times more frequent than in the entire series (table 4). In part this difference in frequency is an indication that the lesions giving rise to two infarcts are more apt to be fatal than those causing single infarcts. This is in accord with past experience.¹³ In part the difference may be due to the occasional difficulty of establishing a correct diagnosis from the electrocardiograms. We classified cases in which autopsy was not performed as belonging in this group only when serial curves demonstrated both occlusions (fig 11 *A* and *B*). Since in the cases of combined infarcts demonstrated at autopsy the most recent infarct dominated the final electrocardiographic curve (figs 5 and 6 *B*), it is probable that in a number of cases in which autopsy was not done and in which there was more than one infarct either the condition was classed as a single anterior or posterior infarct or the case was rejected from the series because the diagnosis was not established. This is a possible source of error in the interpretation of single electrocardiograms.

12 (a) Sprague, Howard B, and Organ Edward S. Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital (1914-1934), New England J Med **212** 903, 1935. (b) Levine and Brown.⁷¹ Appelbaum and Nicolson.⁷² Barnes and Ball.¹⁰¹ Mullins.¹⁰⁶

13 Conner and Holt.^{9b} Master, Jaffee and Dack.¹¹¹ Sprague and Organ.¹²¹

(d) *The Relative Value of the Different Leads in the Diagnosis of Recent Infarction*—In 64 per cent of the entire series of 200 cases the electrocardiograms showed characteristic changes in all four leads in 32.5 per cent there were one or more leads in which the changes were not typical, and in 3.5 per cent there was a single record which though abnormal was not characteristic, the diagnosis being based on the change

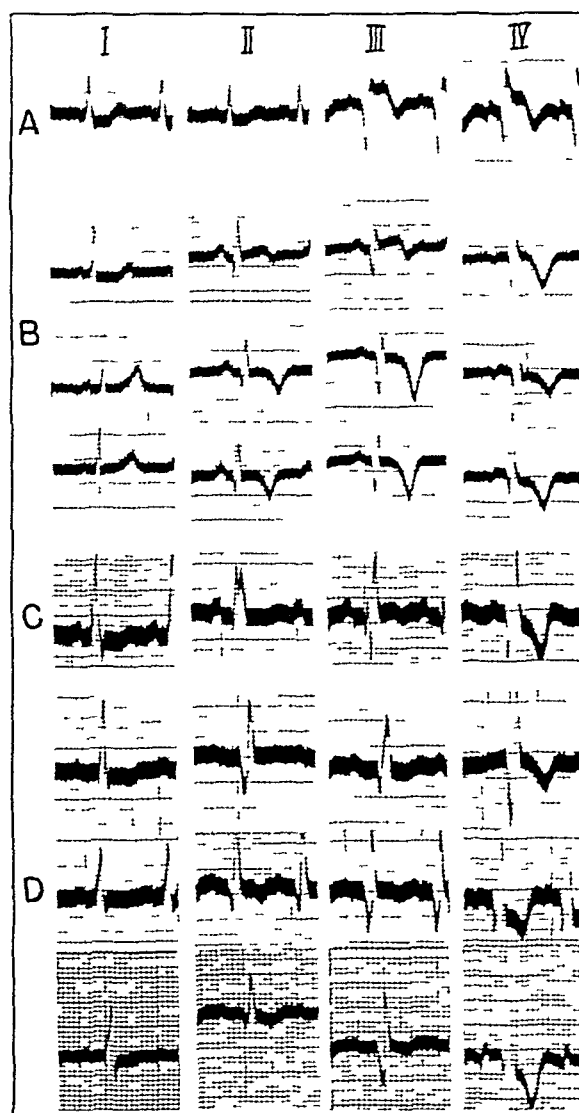


Fig. 4—Electrocardiograms of 3 patients (cases A to C) with infarction of the posterior wall due to a thrombus in the circumflex branch of the right coronary artery. Also electrocardiograms of a patient (case D) with proved infarction of the posterior wall with septal extension due to sclerotic involvement of both coronary arteries. The necropsy reports are summarized in table 3.

Case A		Case B		Case C		Case D	
Attack	5/ 4/36	Attack	7/12/32	Attack	4/ 3/35	Curve taken	
Curve taken	5/ 6/36	Curves taken	8/ 3/32	Curve taken	4/ 9/35	before attack	2/ 1/35
Death	5/ 8/36		8/29/32	Death	7/1 '35	Attack	11/17/35
			9/24/33			Curves taken	11/22/35
		2d attack	9/24/33				11/25/35
		Death	10/ 1/33			Death	11/27/35

observed in the serial curves. In 16 per cent of the cases in which autopsy was performed the electrocardiogram was not characteristic (in all these cases only one record was made [figs 1 to 7, inclusive]). This indicates that we probably failed to recognize instances of recent infarction when only one record was taken¹⁴

In 26 per cent of the 200 cases the conventional leads were not characteristic in single or in serial curves, the diagnosis being based primarily on the changes in lead IV. In only 6.5 per cent were the conventional leads characteristic and lead IV without characteristic changes. The fact that more than a fourth of all the cases might have been overlooked (even in a study of serial curves) if the diagnosis had depended only on the standard three leads shows the value of lead IV and points to the need of taking this lead in all cases of suspected recent infarction. This is particularly true of cases of anterior infarctions, lead IV having established the diagnosis in 30.3 per cent of these instances in our series. Furthermore, lead IV was often of great value in confirming the diagnosis in instances of combined anterior and posterior infarctions. However, lead IV did not establish the diagnosis in 2.5 per cent of the cases of anterior infarction and in 12.3 per cent of the cases of posterior infarction. In cases of posterior infarction lead III was frequently the lead which determined the diagnosis early.

14. On the other hand, we noted 1 case in which autopsy failed to show infarction and in which infarction was indicated clinically and electrocardiographically two years before death (fig 10 C). This patient at autopsy showed only narrowing of both coronary arteries, but no occlusion or myocardial infarction could be seen. Whether we were dealing with disseminated small infarcts (Buchner, F., Weber, A., and Haager, B. *Koronarinfarkt und Koronarinsuffizienz*, Leipzig, Georg Thieme, 1935; Buchner, F., and von Lucadou, W. *Electrocardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimentellen Koronarinsuffizienz*, *Beitr z path Anat u z allg Path* **93** 168, 1934) is problematic. Small multiple infarcts do occur (viz., cases illustrated in figure 8 A and B). When they heal, the scars which form, it seems to us, would be difficult to distinguish post mortem from fibrosis which gradually develops without infarction, yet the electrocardiogram would show the localized ischemia (Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W. *The Electrocardiographic Changes in Myocardial Ischemia*, *Am Heart J* **6** 522, 1931; Katz, L. N., and Wallace, A. W. *The Role of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram*, *Am J M Sc* **181** 836, 1931; Kountz, W. B., and Hammonda, M. *The Effect of Asphyxia and of Anoxemia on the Electrocardiogram*, *Am Heart J* **8** 259, 1932; Rothschild, M. A., and Kissin, M. *Induced General Anoxemia Causing R-T Deviation in the Electrocardiogram*, *ibid* **8** 745, 1932) and would have a time course similar to that in cases of confluent infarction. We have noted another case in which there were suggestive changes but coronary involvement was not observed at autopsy. Here the changes seen in the electrocardiogram (fig 8 C) were probably associated with the moribund condition of the patient at the time the records were taken.

Digitalis in large doses tends to modify the form of the electrocardiogram,¹⁵ but in only 9 per cent of our series of 200 cases was digitalis given, usually in too small quantities to interfere with the electrocardiographic interpretation. In fact, it was found that in only 1 case had large quantities of digitalis been given with resulting confusion (fig 1 H).

Intraventricular block was another disturbing element in the evaluation of the electrocardiographic changes,¹⁶ as was also the effect of old, long-standing coronary insufficiency. In these instances serial curves are of great value. Pericardial involvement also may distort the elec-

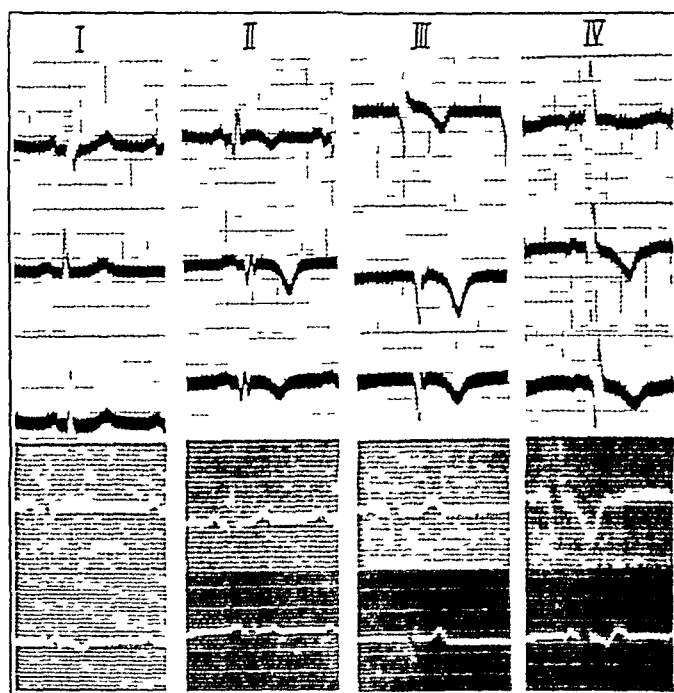


Fig 5—Electrocardiograms of a patient with proved old infarction of the posterior wall and recent infarction of the anterior wall. The necropsy reports are summarized in table 3.

First attack	7/20/32	Second attack	12/ 8/33
Curves taken	8/ 3/32	Curves taken	12/ 9/33
	8/27/32		12/20/33
	9/19/32	Death	12/23/33

15 DeGraff, A. C., and Wible, C. L. Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, *Proc Soc Exper Biol & Med* 24 1, 1926. Brams, W. A., and Gaberman, P. The Effect of Digitalis on the T-Wave of the Electrocardiogram. An Experimental Study in Human Beings, *Am Heart J* 6 804, 1931. Strauss, H., and Katz, L. N. Effect of Digitalis on the Appearance of Lead IV, *ibid* 10 204, 1935.

16 Salcedo-Salgar, Jorge, and White, Paul D. The Relationship of Heart-Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis, *Am Heart J* 10 1067, 1935. Ball, David. The Occurrence of Heart-Block in Coronary Artery Thrombosis, *ibid* 8 327, 1932. White²¹

tiocardiogram¹⁷ Pulmonary embolism also caused difficulties, and we have recently observed 2 cases in which the electrocardiographic distortion was due to nonpenetrating thoracic trauma The problem of differentiating cardiac insufficiency on the basis of advanced coronary sclerosis from abrupt coronary closure was met with a number of times and was not always easy to solve Again we have found, as we pointed out in a previous communication,¹¹ that in a case of chronic coronary insufficiency a single record may show a picture (fig 10 *A*) similar to that seen in cases of abrupt coronary closure, serial curves, however, will fail to show the regression indicative of healing seen after an infarct develops

(*e*) *Abnormalities in Standard Three Leads in Cases of Recent Infarction*—Our analysis of these changes are summarized in table 4 and are illustrated by serial curves in figures 12 *A*, 13, 14 and 17 and by the curves for the cases in which autopsy was performed (figs 1 to 7) The following points merit emphasis

1 Abnormalities of rhythm occurred occasionally, especially in cases of the anterior type of infarct (figs 1 *H*, 2 *A*, curve 3, and 2 *C*)

2 Intraventricular block occurred especially in cases of combined infarcts (figs 6 *A* and *B* and 7 *C*) It was observed also in 3 cases of anterior infarction in which autopsy was performed (figs 1 *F* and *G* and 2 *D*) Thus while septal infarction occurred in 64 per cent of all cases in which autopsy was performed (table 3), electrocardiographic evidence of intraventricular block occurred in only 40 per cent of these same cases However, septal infarcts do not always lead to intraventricular block, as shown by our group of cases in which autopsy was performed, especially those in which the condition involved only the apex or the lowest third of the septum In the present series there was 1 case of intraventricular block without septal infarction (fig 6 *B*), probably on the basis of old coronary sclerosis Intraventricular block often masks the features of the electrocardiogram commonly seen with infarction (figs 1 *F*, curve 2, and 2 *D*) Often, despite the block, changes occur which indicate an occlusion, especially when serial curves are obtained At all events, a succession of changes or the presence of transitory block is to be viewed as suggestive

17 Scott, R W, Feil, H S, and Katz, L N Electrocardiogram in Pericardial Effusion I Clinical, *Am Heart J* 5 68, 1929 Katz, L N, Feil, H S, and Scott, R W Electrocardiogram in Pericardial Effusion II Experimental, *ibid* 5 78, 1929 Barnes, A R Electrocardiographic Pattern Observed Following Coronary Occlusion Complicated by Pericarditis, *ibid* 9 734, 1934

3 Low "voltage" in the conventional leads was a frequent finding especially with recent anterior infarcts,¹⁸ and was not usually associated with low voltage in lead IV (figs 1 *A* to *D*, *G*, *H*, 2 *B* and *D* and 3 *C*) At times this low voltage was transitory

4 Slurring or notching of QRS occurred in almost all cases

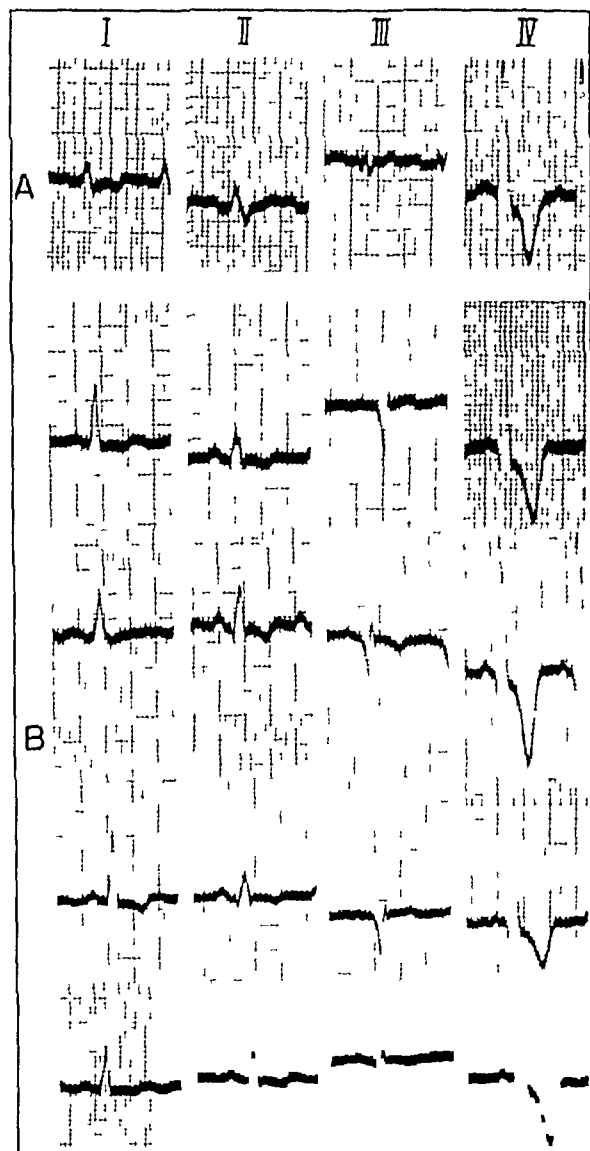


Fig 6—Electrocardiogram of a patient (case A) with proved old infarction of the anterior wall and recent infarction of the posterior wall and electrocardiograms of a patient (case B) with proved old infarction of the anterior wall and more recent infarction of the posterior wall (about two months old at the time of death) The necropsy reports are summarized in table 3

Case A		Case B	
Attack	2/19/36	First attack	1/1/36
Curve taken	2/20/36	Curve taken	2/6/36
Death	2/26/36	Second attack	2/11/36
		Curves taken	1/14/36, 2/23/36, 4/15/36
		Death	4/27/36

18 Steuer, L. G. The Electrocardiogram of Low Voltage. A Report of Fifty Autopsied Cases, *Am Heart J* 9:405, 1934

5 Left axis shift occurred with all types, but the marked deviation associated with preponderance of the left ventricle was more common with posterior infarction (table 4) On occasion this was transitory¹⁹

6 Right axis shift was infrequent and in our series occurred only with anterior infarction On occasion it was transitory

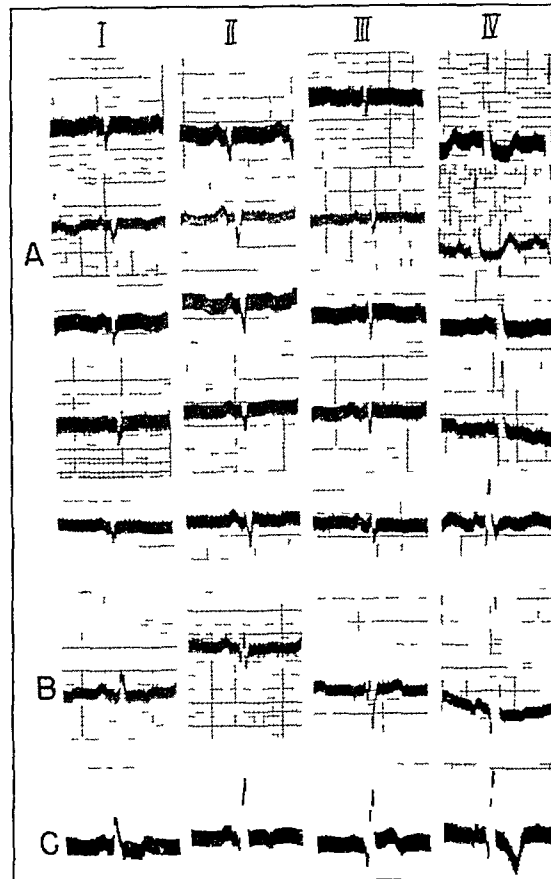


Fig 7—Electrocardiograms of 2 patients (cases A and B) with proved old infarction of the posterior wall, with more recent infarction of the anterior wall, the latter due in both cases to the occurrence of thrombi in the left anterior descending coronary artery a few months before death The third electrocardiogram is that of a patient (case C) with proved old infarction of the anterior wall due to an occluding plaque in the left anterior descending coronary artery and an old and more recent infarction of the posterior wall due to old narrowing and a recent thrombus in the right coronary artery In all 3 cases there were aneurysms in the infarcted areas The necropsy reports are summarized in table 3

Case A		Case B		Case C	
Attack	2/ 7/36	Attacks of pain for two years		Attacks of pain for several years	
Curves taken	3/ 5/36	Last attack	10/19/32	Last attack	1/18/34
	3/11/36	Curve taken	10/25/32	Curve taken	1/19/34
	4/ 9/36	Death	10/31/32	Death	1/20/34
	4/27/36				
	5/ 5/36				
Death	5/ 8/36				

19 Bartels, E C, and Smith, H L Gross Cardiac Hypertrophy in Myocardial Infarction, Am J M Sc 184 453, 1932

7 Deviations in the ST segment were not always characteristic. With anterior infarction the classic change is said to be an elevated ST segment in lead I (fig 15). In our series depression of the ST segment in lead I was more than twice as common as elevation of this segment with anterior infarction (series A, table 4). In 6 of the 8 cases in which autopsy was performed recent anterior infarctions due to thrombotic closure had an elevated ST₁ (fig 1 *A* to *D*, *F* and *G*), while those due to closures resulting from sclerotic plaques did not show any elevation of ST. In fact, in 5 of 7 of the latter cases ST₁ was depressed (figs 2 *A*, *B* and *D*, and 3 *A* and *B*, table 4, series C). In the entire series of cases of posterior infarction the classic picture of depression of ST₁ was common (table 4, series A) and occurred in every case in which autopsy was performed (fig 4 *A* to *D*), an elevated ST₁ occurred

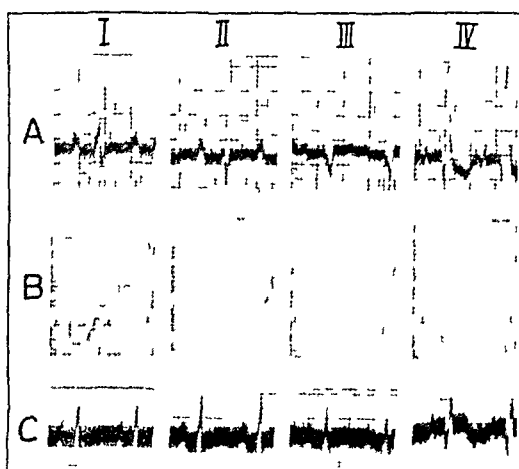


Fig 8—Electrocardiograms of 2 patients (cases A and B) with multiple small infarctions. Both coronary arteries had sclerotic plaques. Necropsy reports are summarized in table 3. In case C autopsy showed no infarction or coronary involvement even on microscopic examination, so the electrocardiographic changes may be explained as probably due to terminal ischemia of the myocardium of a dying patient.

Case A	Case B	Case C
Repeated attacks of pain for fifteen months	Vague cardiac pain for several years	Prostatectomy 11/25/33
Severe attack 12/31/35	Severe attack 12/ 3/34	Curve taken 12/15/33
Curve taken 1/ 7/36	Curve taken 12/ 4/34	Death 12/15/33
Death (pulmonary embolism) 1/16/36	Death 12/13/34	

in only 5.5 per cent of the entire series of cases of posterior infarction. Of the 6 cases of combined infarcts in which autopsy was performed, the ST₁ segment was depressed in 4 (figs 6 *A* and *B* and 7 *B* and *C*) and was unchanged in the other 2 (figs 5 and 7 *A*). The changes in the ST segment in lead II were extremely variable. The classic picture of elevation of ST in lead III with posterior infarction was common in the entire series (table 4, series A) and occurred in all the cases of this type of infarction in which autopsy was performed (fig 4 *A* to *D*). How-

ever, in 68 per cent of the cases of posterior infarction in the entire series the ST segment in lead III was depressed (table 4, series A). With the combined type there was elevation of ST₃ in 2 cases in which autopsy was performed (figs 6 B and 7 C). These were cases in which a more recent posterior infarct was due to a thrombus in the right coronary artery. The classic picture of depression of the ST segment in lead III with anterior infarction occurred in only 26.9 per cent of the entire series, and in an almost equal number (25.2 per cent) the ST segment was elevated in this lead (table 4, series A). The series of cases in which autopsy was performed demonstrate that the elevation of ST₃

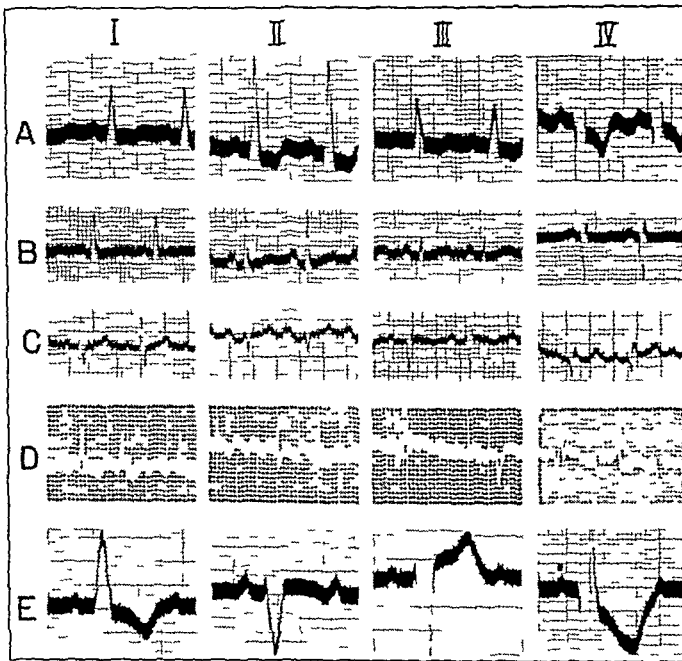


Fig 9—Electrocardiograms of 5 patients (cases A to E) with proved coronary sclerosis without infarction. The necropsy reports are summarized in table 3.

Case A		Case B		Case C	
Attack	11/ 5/35	Operation	9/ 7/35	Herniotomy	2/ 6/35
Curve taken	11/21/35	Curve taken	9/10/35	Curve taken	2/13/35
Death	11/24/35	Death	9/18/35	Death	2/22/35
Case D		Case E			
Cholecystectomy	7/ 9/35	Curve taken			2/24/34
Severe pain	8/23/35	Death (perforated duodenal ulcer)			4/ 9/36
Curve taken	9/10/35				
Death	9/16/35				

with anterior infarction was noted when closure was due to sclerotic plaques, with involvement of both the right and the left coronary artery (figs 2 D and 3 A). In both cases there was intraventricular block.

It may therefore be concluded from the analysis of cases in which the diagnosis was verified at autopsy that (1) the changes observed

in the ST segment fit the classic picture closely in cases of recent anterior or posterior infarction due to thrombotic closure and that (2) the deviations observed in the ST segment are variable in cases in which autopsy shows recent anterior infarction due to closure caused by sclerotic plaques. Apparently the variability in the changes in the ST segment with recent anterior infarction due to closure caused by sclerotic plaques is to be attributed to an insufficient coronary blood

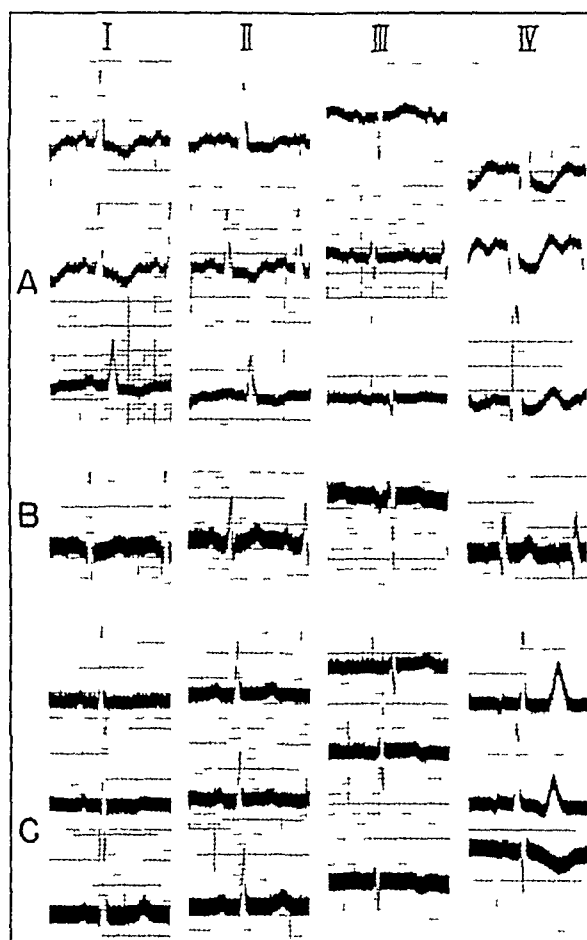


Fig 10—Electrocardiograms of 3 patients (cases A to C) with proved coronary sclerosis without infarction, resembling electrocardiograms of patients with infarction of the anterior wall. The necropsy reports are summarized in table 3. Case C is particularly interesting, since the clinical course in 1934 also indicated infarction.

Case A		Case B		Case C	
Curves taken	6/26/35	Prostatectomy	11/26/35	Curves taken	2/ 3/34
	7/ 1/35	Pain in left side of chest	12/ 7/35		2/10/34
	7/29/35	Curve taken	12/27/35		2/25/34
Death (malignant nephrosclerosis)	8/ 2/35	Death (pulmonary embolism)	12/30/35	Cerostomy	/ 1/36
				Death	3/ 1/36

supply to the posterior wall of the left side of the heart consequent on the diffuse coronary sclerosis in these cases. In the cases of closure due to sclerotic plaques the autopsy reports showed that the coronary

sclerosis was more extensive than in the cases of thrombotic closure and that the occluding plaques were often present in more than one artery (table 3)

The deviation of the ST segment in the classic picture^{7b} is opposite in direction to that of the T wave. This deviation of the ST segment is often associated with bowing which points away from the peak of the T wave. According to the findings in cases in which autopsy was performed, this bowing appears in the earliest stages of the infarcts which are due to thrombosis but quickly disappears. With recent anterior infarction this bowing is up in lead I and down in lead III, with recent posterior infarction it is just the reverse (fig 15). While the majority of the deviations in the ST segment tend to fit this picture, exceptions do occur, especially in cases of recent anterior infarct due to closure caused by sclerotic plaques. We have found further that, as has been shown in animal experiments,²⁰ the ST segment may be depressed in all three leads (fig 2A, curve 2) but is rarely elevated in all.

8 The coronary T wave, which may be positive or negative, as we have pointed out elsewhere,²¹ is characterized by symmetrical limbs, rounded shoulders and a sharp peak,^{7c} which may be associated with bowing and deviation of the ST segment in a direction opposite to that of the T wave^{7b}. With recent anterior infarction the classic picture is a negative T wave in lead I and a positive T wave in lead III, with recent posterior infarction the direction of T in these leads is the reverse. The dominant T wave is found to occur during healing in the infarcted area.

A negative T_1 occurred in the majority of cases of recent anterior infarcts (table 4, series A), however, in approximately a fourth of these cases T_1 was upright.²² A negative T_1 occurred only rarely with recent posterior infarction. A negative T_2 occurred in most instances of recent posterior infarction and was seen in every case in which the

20 Korey, H, and Katz, L. N. The Electrocardiographic Changes Produced by Injuries of Various Parts of the Ventricle, *Am J M Sc* **188** 387, 1934. Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch Int Med* **22** 8 (July) 1918. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C. Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *Am Heart J* **7** 627, 1932. DeWart, A., Storm, C. J., and Koumans, A. K. J. Ligation of the Coronary Arteries in Javanese Monkeys, *ibid* **11** 676, 1936. Abramson, D. I., Shookhoff, C., and Fenischel, N. M. Study of Variations of RS-T Segment in Experimental Ventricular Trauma, *ibid* **12** 174, 1936. Wood and Wolferth.^{4c}

21 Bohning, A., and Katz, L. N. Unusual Changes in the Electrocardiogram of Patients with Recent Coronary Occlusion, *Am J M Sc* **186** 39, 1933.

22 In these instances lead IV was the characteristic feature (figs 12B and 16A).

lesion was present at autopsy (fig 4) In approximately a sixth of the entire series of cases of recent posterior infarction, T_1 was upright A negative T_2 occurred in 92 per cent of the cases of recent anterior infarction (table 4, series A) In the cases in which this lesion was present at autopsy, a negative T_2 occurred in only some of those in which the infarct was due to closure caused by sclerotic plaques (fig 3 *A* to *C*), and it was not a typical coronary T wave A negative T_2 was more often present with a negative T_3 than with a negative T_1

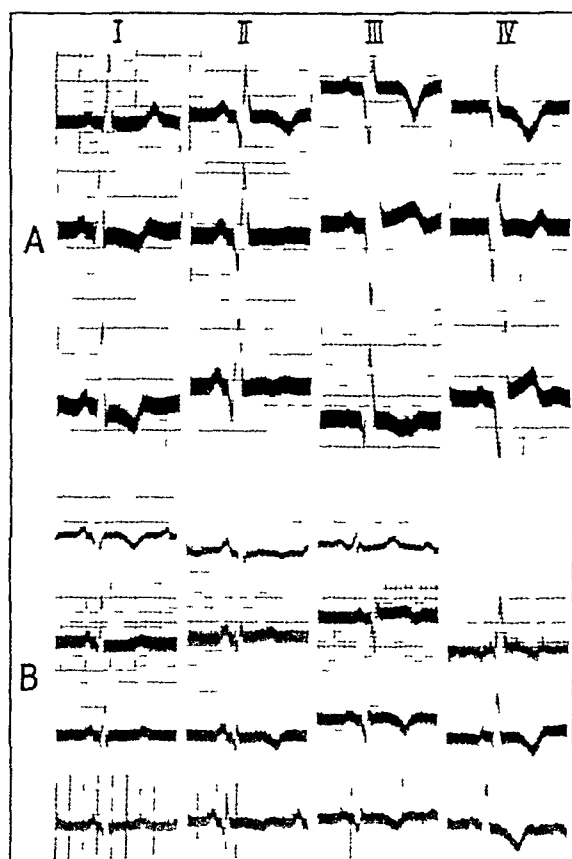


Fig 11—Electrocardiograms of a patient (case A) with case of combined infarction suggesting an old infarction of the posterior wall and more recent infarction of the anterior wall and electrocardiograms of a patient (case B) with combined infarction suggesting an old infarction of the anterior wall and a more recent infarction of the posterior wall

	Case A		Case B
First attack	2/ 1/34	First attack	3/12/33
Curve taken	3/ 8/34	Curve taken	4/ 9/33
Second attack	3/ 1/35	Second attack	12/15/32
Curves taken	5/15/35	Curves taken	12/16/32
	1/ 2/36		12/29/32
Alive	6/ 1/36		1/26/33

Coronary T waves were more frequently seen when the waves were negative than when they were positive but the reverse was true in several instances (figs 4 *A* and *B*, 5 and 12 *B*) The changes in the T wave tended to conform with the classic picture, although exceptions

were not unusual, especially with anterior infarction due to closure caused by sclerotic plaques. A negative coronary T wave in all three leads did occur (fig 14), but a positive coronary T wave in all three leads was rarely found.

9 The classic concept²³ in regard to the Q wave (the term applied to the first negative phase of a diphasic QRS complex which is a fourth or more of the height of the major upright phase) and the S wave (a diphasic QRS complex with a negative second phase) was not confirmed in our series.

In our cases in which autopsy was performed the classic Q₁ occurred with recent anterior infarction due to thrombotic closure (fig 1), but not in that due to closure with sclerotic plaques (figs 2 and 3). A Q₁ did not occur in cases of recent posterior infarction (fig 4).

In our cases in which autopsy was performed the classic Q₃ occurred in all instances of recent posterior infarction (fig 4), but it occurred also in 3 instances of recent anterior infarction due to thrombotic closure (fig 1 C, D and H). A Q₃ was also present in 3 cases of combined infarction shown at autopsy (figs 5, 6 B and 7 C). A Q wave was found in all three leads on occasion (fig 11 B).

The diagnostic value of Q₃ in the localization of infarcts is thus practically nil, and it is doubtful whether Q₁ is of greater value in this regard. Statistical studies have shown that Q₃ is found with a variety of types of chronic myocardial involvement other than infarction.²³ The weight of evidence seems to show that Q₃ indicates disease of the left ventricle, whether or not accompanied with recent (or old) infarction.²⁴ No significance could be attached to the occurrence of S₁ and S₂ in our series, except that S₃ never occurred in any cases in which recent

23 Bland, E. F., and White, P. D. The Clinical Significance of Complete Inversion of Lead III in the Human Electrocardiogram, *Am Heart J* **6** 333, 1931. Kossman, C. E., Shearer, M., and Texon, M. Initial Ventricular Deflection in Electrocardiogram of Normal Subjects, *ibid* **11** 346, 1936. Willis, F. A. Occurrence and Significance of Electrocardiograms Displaying Large Q-Wave in Lead III, *ibid* **6** 723, 1931. Edeiken, J., and Wolferth, C. C. Significance of Deep Q in Lead III, *ibid* **7** 695, 1932.

24 Pardee, H. E. B. The Significance of an Electrocardiogram with a Large Q in Lead III, *Arch Int Med* **46** 470 (Sept.) 1930. Goldbloom, A. A., and Kromer, M. L. The Clinical Significance of the Deep Q-Wave in Lead III, *M Clin North America* **15** 1345, 1932. Wallace, A. W. The Q-Wave in the Electrocardiogram, *Am J M Sc* **187** 498, 1934. Feldman, L. The Initial Ventricular Complex of the Electrocardiogram in Coronary Thrombosis, *Ann Int Med* **9** 1714, 1936. Strauss, Sidney and Feldman, L. The Significance of Deep Q and Lead III, *Am J M Sc* **185** 87, 1933. Durant, T. M. The Initial Deflections of the Electrocardiogram in Coronary Disease, *ibid* **188** 225, 1934. Ziskin, T. Clinical Significance of the Electrocardiogram with Large Q in Lead III, *Arch Int Med* **50** 435 (Sept.) 1932. Barnes⁷⁵

posterior infarction was noted at autopsy. No particular significance could be attached to the occurrence of the combination of Q_1 and S_1 or of Q_2 and S_1 in our series. The analysis of cases of proved recent infarction in our series and in the series of cases for which autopsy reports have been published does not support the concept that the Q and S waves are of much value in the diagnosis of recent infarction.

10. Further evidence of the reliability of the foregoing findings was afforded by a review of all the previously published electrocardiograms

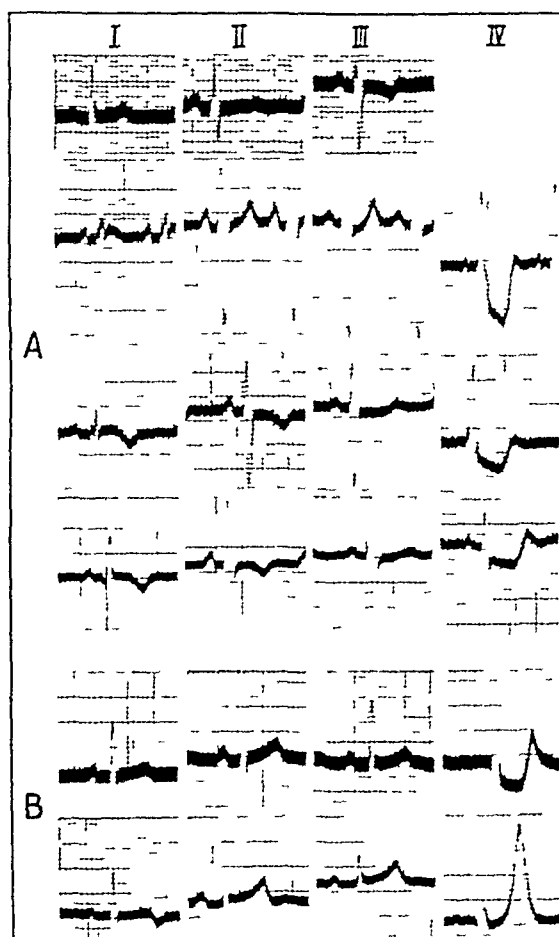


Fig. 12—Electrocardiograms of 2 patients with recent anterior infarction. The serial curves in case A illustrate the classic type of change, especially early changes. Those in case B show marked changes in the T wave in lead IV.

Case A		Case B	
Curve taken before attack	8/ 9/32	Attack	9/ 1/36
Attack	2/16/34	Curves taken	9/14/36
Curves taken	2/17/34		10/ 5/36
	3/ 2/34		
	11/13/34		
Death (no autopsy)	10/13/34		

made in cases in which adequate autopsy reports of myocardial infarction were given. In some reports the manner of closure of the coronary artery, whether due to a fresh thrombus or to a sclerotic plaque, is not

designated, nor is the condition of the coronary arteries and myocardium adequately described. It is in such reports that statements are most often made that the changes in three lead electrocardiograms do not fit into the classically described criteria for anterior and posterior infarcts. On the other hand, there is an increasingly large literature with complete and carefully recorded clinical and necropsy data, which is of great value for correlations such as we have attempted. In checking over these published reports we have noted that the three lead electrocardiograms which fit the classically described types for recent anterior and recent posterior infarction most closely are almost invariably found in instances of a suddenly occluding coronary thrombus uncomplicated by old chronic lesions of the myocardium. The less typical three lead electrocardiograms occur in the group of reported cases in which the data show definite evidence of occluding sclerotic plaques or advanced sclerosis of both coronary arteries, with long-standing myocardial involvement. This confirms our own observations and emphasizes the importance of complete and accurate autopsy data in such cases.

(f) *Abnormalities in Lead IV with Recent Infarction*—Our analysis of these changes is summarized in table 5. The following are the more significant findings:

1. A positive P wave was found more often in this series of cases than the normal negative or diphasic P_4 , at times this positive P wave was transitory. However, the positive P wave was found associated with lesions other than coronary occlusion.

2. The presence or absence of the Q wave, the first negative phase of the QRS complex, has had considerable significance attached to it.²⁵ The absence of Q_4 has been stated to be characteristic in cases of recent anterior infarction. This is fairly well borne out in our cases in which autopsy was performed, in all cases of recent anterior infarction due to thrombotic closure this wave was absent (fig. 1), and in only 4 of the cases due to closure caused by sclerotic plaques was a small Q_4 wave seen (figs. 2 C and 3 A to C).

In the 4 cases of recent posterior infarction, on the other hand the Q_4 wave was present (fig. 4 A to C), although it was small in the case associated with closure due to sclerotic plaques (fig. 4 D). It is noteworthy that Q_4 was present in all 6 cases of combined anterior and

²⁵ Levine, Harold D., and Levine, Samuel A. An Electrocardiographic Study of Lead IV, with Special Reference to the Findings in Angina Pectoris, *Am J M Sc* **191** 98, 1936. Faulkner, J. M. The Electrocardiographic Diagnosis of Acute Cardiac Infarction, with Special Reference to the Value of Precordial Leads, *New England J Med* **213** 1215, 1936. Wilson and others^{1d}. Johnston, Hill and Wilson^{2a}. Wilson, Hill and Johnston^{3b}.

posterior infarcts (figs 5, 6 *A* and *B* and 7 *A* to *C*), even when the anterior infarct was the more recent (fig 5) In the entire series, Q_1 failed to occur in a little more than half the 119 cases of recent anterior infarction, it was present in all 8 cases of combined infarction and was absent in only 6.8 per cent of the 73 cases of recent posterior infarction

While the absence of Q_1 seems significant in cases of recent anterior infarction due to thrombotic closure, its presence does not rule out a recent anterior infarct Furthermore, it must be borne in mind, as we

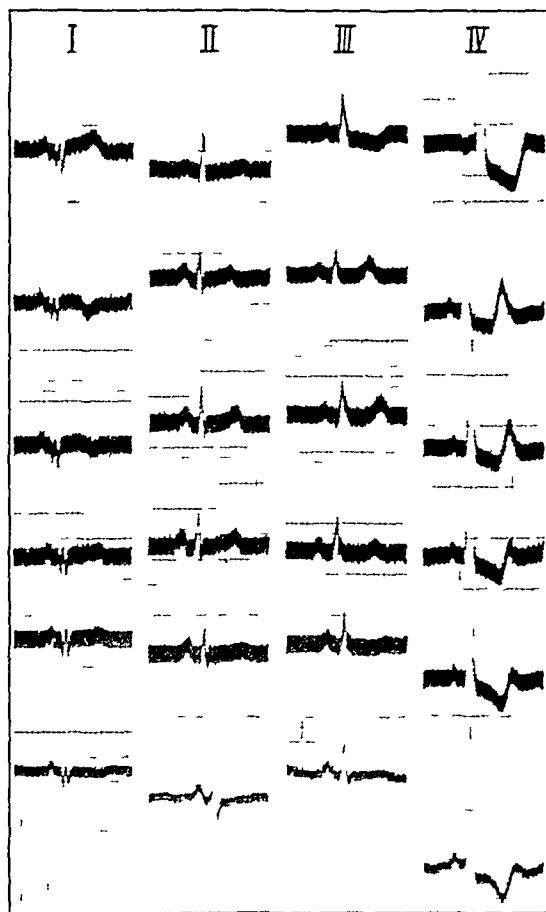


Fig 13—Electrocardiogram of a patient with anterior infarction The serial curves illustrate the classic type of change and the late stages of recovery

Attack	5/ 8/35	Curves taken	10/23/35
Curves taken	5/15/35		11/26/35
	6/12/35		2/21/36
	7/11/35	Alive	6/ 1/36

have reported before²⁶ that Q_4 may be absent when there is no infarction and even when there is no coronary disease

3 The QRS complex, aside from a few instances of W-shaped or M-shaped complexes (usually associated with intraventricular block²⁶),

²⁶ Edeiken, J, and Wolferth C C Clinical Significance of M and W Shaped QRS Complex in Lead II of the Electrocardiogram, *Am J M Sc* 188 842, 1934

was either monophasic and positive or diphasic. The diphasic QRS_1 had a negative first phase in most instances, but in a few the positive phase was first. Some of the diphasic QRS_4 complexes were mainly up, and a few were mainly down. As might have been anticipated from our discussion of the Q_4 wave, in all cases of proved recent anterior infarction due to thrombotic closure there was a monophasic upright QRS_4 (fig 1), whereas in cases of recent anterior infarction proved to be due to closure caused by sclerotic plaques QRS_4 was not always monophasic (however, when not monophasic it was mainly up, figs 2 and 3). In only 1 case of recent posterior infarction due to closure caused by sclerotic plaques was there a mainly upright QRS_4 (fig 4D). In the entire series QRS_4 was mainly or entirely up in about 75.7 per cent of the cases of recent anterior infarction and in only 12.3 per cent of the cases of recent posterior infarction (table 5). A mainly upright QRS_4 was also common with combined infarction. A mainly negative QRS_4 was found occasionally in cases of recent posterior infarction and was often transitory. The few instances in which there was a diphasic QRS_1 with a positive first phase occurred only in cases of recent anterior infarction and then this complex was sometimes associated with intraventricular block (fig 1F, curve 2, and G, curve 2).

In brief, this study indicates that a monophasic upright QRS_4 is characteristic of recent anterior infarction due to thrombotic closure but may occur in cases of infarction due to closure caused by sclerotic plaques. Furthermore, it must be borne in mind that an entirely or mainly positive QRS_4 occurs in cases of extensive coronary sclerosis without infarction (figs 9A and 10A and C), as we have shown previously.¹¹ It may therefore be a sign of extensive myocardial change and not necessarily of recent (or old) infarction.

4 Deviations in the ST segment were much more characteristic than the changes in the QRS complex. Elevation of ST_4 was seen in only 2 cases in which autopsy was performed and both were cases of recent posterior infarctions (fig 4A and B). Elevation of ST_4 occurred in 58.9 per cent of the entire series of cases of recent posterior infarction, in 3 of the 8 cases of combined infarction and in only 5.1 per cent of the entire series of cases of recent anterior infarction (table 5). Our study showed further that when ST_4 was elevated it tended to become horizontal, and its termination was more clearly to be differentiated than in the normal downward sloping ST_4 (fig 4A). This horizontal ST_4 often occurred without elevation, and we consider this a characteristic finding with recent posterior infarction (fig 4B).

A deeply negative ST_4 (more than 2 mm) occurred in all but 1 of the cases of proved recent anterior infarction due to thrombotic closure (fig 1), in 1 of the 6 cases of proved combined anterior and

posterior infarctions (fig 6 *A* and *B*) and in 1 of the 4 cases of proved recent posterior infarction (fig 4 *D*), in the last-mentioned case the infarct was due to closure caused by sclerotic plaques and both coronary arteries showed advanced changes. In the entire series, a negative ST_1 of more than 2 mm occurred in about 39.5 per cent of the cases of recent anterior infarction and in only about 6.8 per cent of the cases of recent posterior infarction (table 5).

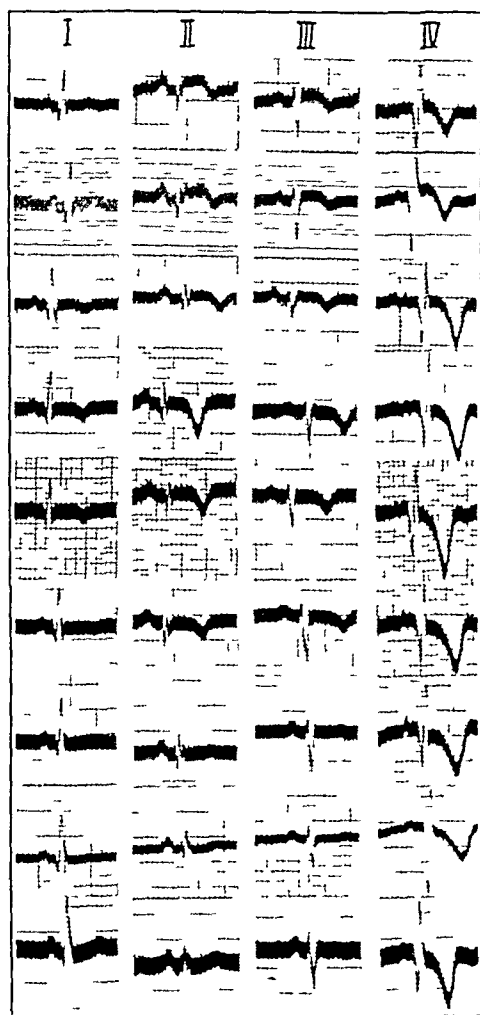


Fig 14—Electrocardiograms of a patient with recent posterior infarction. The serial curves illustrate the classical type of change.

Attack	8/12/32	Curves taken	10/22/32
Curves taken	8/17/32		2/25/34
	8/19/32		10/10/34
	8/26/32		3/26/36
	9/ 8/32	Alive	8/ 1/36
	9/15/32		

5 The T wave was characteristic in the majority of cases. A positive or diphasic T_4 was found in 40 per cent of the cases of proved recent anterior infarction (figs 1 *C*, *D*, *F* and *G* and 2 *A* to *D*) and not once in cases of proved recent posterior infarction. In the entire

series of 200 cases, positive and diphasic T waves were found in 77.3 per cent of the cases of recent anterior infarction and in only 9.6 per cent of the cases of recent posterior infarction. A T_4 within normal limits was found most often in cases of recent posterior infarction and of combined infarctions, and a deeply negative T_4 was found particularly in cases of recent posterior infarctions.

6. Thus, as in the case of the standard three leads, so in lead IV, in the cases in which autopsy was performed the recent infarctions due to thrombotic closure give more characteristic changes than those due to closure caused by sclerotic plaques. In all instances of recent infarction the changes in the ST segment and the T wave of lead IV are more informative than the changes in the QRS complex. Inspection of lead IV in other series of cases in which autopsy was performed shows that the facts here presented can be demonstrated also in these series. No one feature of lead IV can be considered an infallible sign of the type of infarction, although certain deviations of ST_4 and T_4 are fairly characteristic. Lead IV should be viewed in toto and should always be correlated with the standard three leads when a particular interpretation is being made, and the interpretation should be checked with serial curves.

(g) *The Value of Serial Four Lead Electrocardiograms in Cases of Recent Infarction*—Our experience has shown that serial curves are often necessary before a final diagnosis can be made, and they are always helpful in estimation of the natural process and rate of progress of healing in the infarcted area and, perhaps as important as this, in determination of the amount of chronic coronary insufficiency remaining after the healing process has stopped. For these reasons we have paid particular attention to serial curves and have attempted a systematic electrocardiographic follow-up. This was not possible in every case. We were not able to follow through completely enough to obtain the entire series of electrocardiographic changes in all instances. Often it was difficult to obtain a curve immediately after the attack, because the patient was not hospitalized for several hours or days, but we have obtained a number of early curves. Again, it was not always possible to obtain records in the late stage of recovery, which sometimes extends over many months. However, we obtained a sufficient number of curves to be able to depict the usual course of these changes. On the basis of all these records, we have been able to reconstruct an idealized pattern of the succession of changes occurring with recent anterior infarction and those occurring with recent posterior infarction (fig. 15). No one series actually shows all these changes. Differences obviously exist from case to case (compare figs. 12 to 17). One should study the actual records

individually to see how the deviations in the electrocardiograms of different patients vary from the classic picture shown diagrammatically in figure 15. We have data for many other cases in which serial curves illustrate in one record or another all these changes, but space permits presentation of only a few. Figure 15 depicts merely the generalized pattern which is most common. On the evidence obtained from our own cases and from previously published reports of cases in which autopsy was performed, we have concluded that the characteristic picture shown in figure 15 occurs with recent infarction due to a sudden or thrombotic closure and that deviations from this picture are more likely to occur with infarction due to slowly occurring closure or closure caused by sclerotic plaques. No attempt has been made in the graph (fig 15) to give the time values between stages as the time span is an individual affair and varies widely. This is not surprising in view of the wide differences in the degrees of change within the myocardium and the variations in the recuperative efficiency of the coronary circulation of different hearts. The striking changes in the ST segment usually disappear rapidly, often in from a few hours to a few days. Obviously in not all cases is the record normal at first, as in figure 15, and in not all cases does it return to the preexisting level. Often, indeed, the record stops short of complete recovery and persists for a long period at one of the later stages.

The changes in figure 15 are for leads I, III and IV, lead II is omitted for clarity and because it is more variable in its appearance than the other leads. The changes in one lead do not always follow the same tempo as the changes in other leads. In some cases of recent posterior infarction the standard limb leads show the first characteristic change, but on the whole infarction is more easily diagnosed early from lead IV. We have also ignored the frequent transitory ebb and flow of fluctuations in electrocardiographic contour seen during the early stages. When several infarcts are present in different localities naturally the development is not so typical. The presence of intraventricular block also confuses the picture, as does to a lesser extent the presence of other preexisting abnormalities that affect the electrocardiogram.

In the early stages of recent coronary occlusion the changes in the ST segment predominate. These have been described before but we have attempted to correlate them and to depict them graphically. It will be seen that in cases of typical anterior infarction ST_1 becomes elevated, with an upward bowing and a rounded shoulder at the beginning of the T wave, and ST_2 is the inverted image of this. ST_3 at this time becomes deeply depressed and often horizontal so that T_4 cannot be made out (fig 15, stage 2). At the same time Q_4 disappears (Q_1 and S_3 may or may not appear, figs 12 A and 13). In cases of poste-

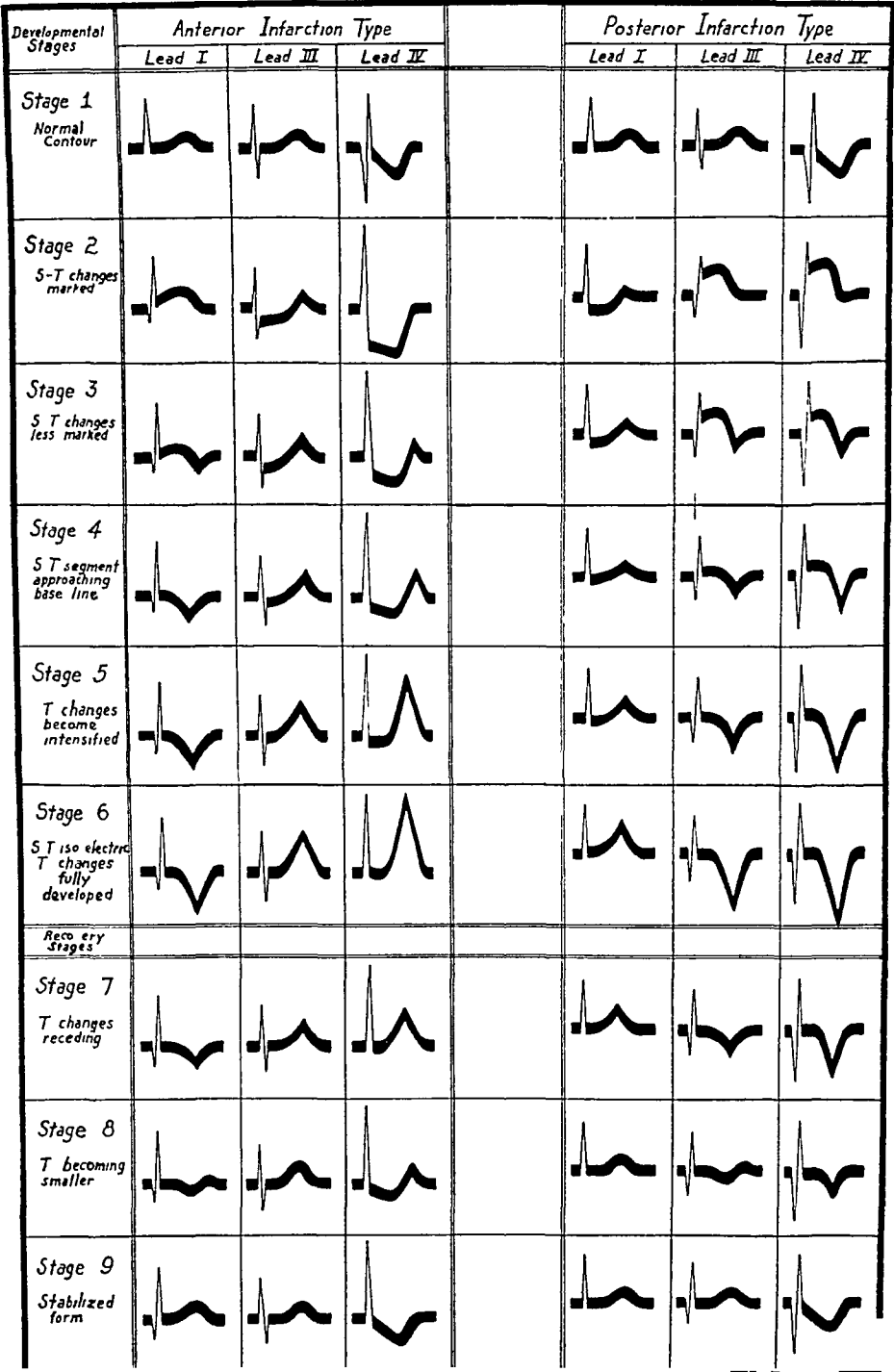


Fig 15—Diagrammatic illustration of classic type of changes usually found in leads I, III and IV in the stages of development of and recovery from uncomplicated infarctions of the anterior and of the posterior wall due to sudden thrombotic closures

in inferior infarction the pictures in leads I and III are the reverse of those in cases of anterior infarction, except that Q_3 is more likely to appear. ST_4 becomes elevated (but not to the degree to which it sinks in cases of anterior infarction) and is horizontal or even bowed upward. As time goes on the ST segment with both types tends to return to the level of the iso-electric line. Later the ST segment loses its bowing in the conven-

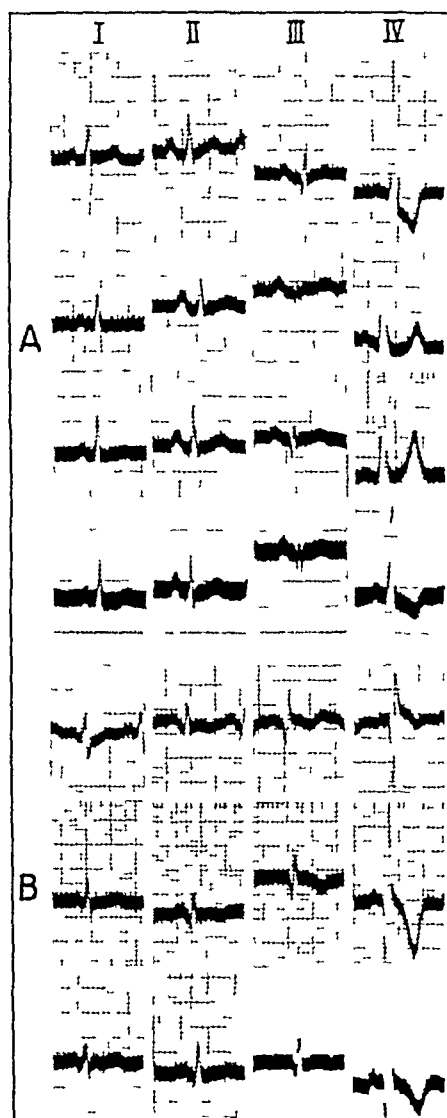


Fig. 16—Serial electrocardiogram of a patient (case A) with anterior infarction in which typical changes occur in lead IV and nondiagnostic changes occur in the conventional leads. Serial electrocardiogram of a patient with posterior infarction in which the changes in lead IV (in ST and T) are typical, whereas the conventional three leads did not definitely establish the diagnosis.

Case A		Case B	
Attack	5/11/34	Attack	8/4/32
Curves taken	5/11/34	Curves taken	8/11/32
	5/22/34		8/15/32
	6/20/34		9/27/32
	9/25/36		
Alive	10/—/36	Dropped dead several months later (no autopsy)	

tional three leads, and a coronary T wave appears in these leads in a direction opposite to that of the original deviation of the ST segment (fig 15, stages 3 to 5, and figs 14 and 17) As we have previously emphasized, whether positive or negative, the coronary T wave is peaked and has symmetrical limbs and rounded shoulders This coronary T wave waxes and becomes the dominant part of the record (fig 15, stage

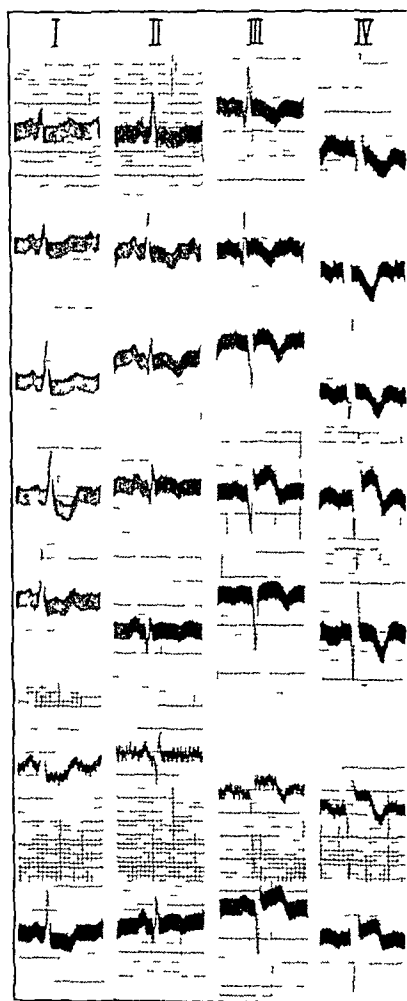


Fig 17—Serial electrocardiograms of a patient with posterior infarction, showing that the frequently recurring attacks of pain were accompanied with definite electrocardiographic changes

Curve taken before attack	10/ 9/35	Curves taken	11/12/35
Attack	10/15/35		12/12/35
Curve taken	10/16/35	Attack	12/27/35
Attack	10/26/35	Curves taken	12/30/35
Curve taken	10/28/35		2/ 4/36
Attack	11/12/35	Alive	6/ 1/36

6) before it wanes again and disappears In cases of anterior infarction as ST_4 returns toward the iso-electric or normally negative level and regains its downward declivity, a diphasic and then a positive T wave

appears, which waxes sometimes to great heights and then wanes and disappears (figs 12 *B* and 16 *A*) In cases of posterior infarction the ST₄ segment returns to the iso-electric or normally negative level (less than 2 mm) and regains its normal downward declivity, usually no clear evidence of infarction remains in this lead unless the T wave is deeply negative (figs 14 and 16 *B*) Nevertheless, serial curves will reveal the progressive waxing and waning of T₄ The later changes (fig 15, stages 7 to 9) are seen in only a limited number of cases In some cases death occurs before these changes are fully developed, in others the electrocardiogram reaches a stationary form and in still others changes occur which may be interpreted (as we have previously shown^{1h}) as indicating a progressive increase in the myocardial involvement due to coexisting progressing coronary disease

Once the deviation in the ST segment disappears and only the deviations in the T wave remain, it becomes difficult to determine from a single record whether the electrocardiogram gives evidence of (*a*) an early stage of recovery after infarction in which T is waxing, (*b*) a late stage of recovery in which T is waning, (*c*) an old infarction or (*d*) chronic coronary insufficiency without infarction Only the past clinical history can distinguish between *c* and *d*, and serial curves are required in order to distinguish *c* and *d* from *a* and *b*, and between *a* and *b*

(*h*) *Speculations Concerning the Value of the Four Lead Electrocardiograms with Various Types of Coronary Insufficiency*—The evidence presented in this report when correlated with that given in our earlier report on coronary sclerosis^{1h} shows that the classification of coronary insufficiency given previously by us^{1h} still holds and can be further amplified Our experience shows that within certain limits serial four lead electrocardiograms can aid in the evaluation of the state and progress of the adequacy of the coronary circulation They can serve to differentiate the transitory acute coronary insufficiency which leads to temporary electrocardiographic deformity without causing permanent injury to the myocardium (figs 8 *C* and 10 *C*) from the more protracted coronary insufficiency which leads to infarction (figs 2 and 3) and the less severe and more chronic forms which cause no infarction (fig 9)

The time course of the different varieties of these forms of coronary insufficiency are depicted diagrammatically with time as the abscissa and the degree of electrocardiographic deviation as the ordinate in figures 19 and 20 The characteristics of the various subgroups are summarized briefly in table 6

In view of the findings in our own studies of cases and the autopsy evidence afforded by these and other cases, we now believe that coronary insufficiency may be subdivided as follows

I Subacute coronary insufficiency

A Uncomplicated forms of recent myocardial infarction (thrombotic closure)

- (a) Anterior
- (b) Posterior

B Complicated forms of recent myocardial infarction

1 Sclerotic closure

- (a) Anterior
- (b) Posterior

2 Combined anterior and posterior infarctions (one recent infarct)

- (a) Old posterior and recent anterior
- (b) Old anterior and recent posterior

3 Multiple recent small infarctions

II Progressive or nonprogressive chronic coronary insufficiency (coronary sclerosis without infarction)

- (a) Distinctive electrocardiogram resembling that with anterior infarction
- (b) Distinctive electrocardiogram resembling that with posterior infarction
- (c) Indeterminate electrocardiogram

III Transitory (acute) coronary insufficiency

IV Suddenly fatal coronary insufficiency (thrombosis, embolism, ventricular fibrillation)

A few words regarding each of these subdivisions are not amiss here. The uncomplicated forms of myocardial infarction consist of the classic types of coronary occlusion which our own and previous autopsy material shows to be due to sudden thrombotic closure (figs 1 and 4 *A* and *C*)

Among the complicated forms of myocardial infarction are those due to the relatively less abrupt occlusion resulting from sclerotic plaques in the coronary arteries. Patients with this form of closure often go through periods of mild heart failure and die when some other complication, such as an operation or pulmonary, renal or cerebral involvement is superimposed. The electrocardiograms are less characteristic, and lead IV is often more diagnostic than the standard three leads (figs 2, 3 and 4 *D*). Another form of complicated myocardial infarction is that in which the presence of several infarcts confuses the electrocardiographic picture (figs 5 to 7, 11 and 18), usually the changes resulting from the most recent infarct are those that dominate the curves. Another form is that in which multiple small infarcts are present

(fig 8) Repeated infarction in the same area is another variety of this last subdivision, each occlusion results in changes in the ST segment of a similar type, which slowly disappear only to reappear again with each new attack (fig 17)

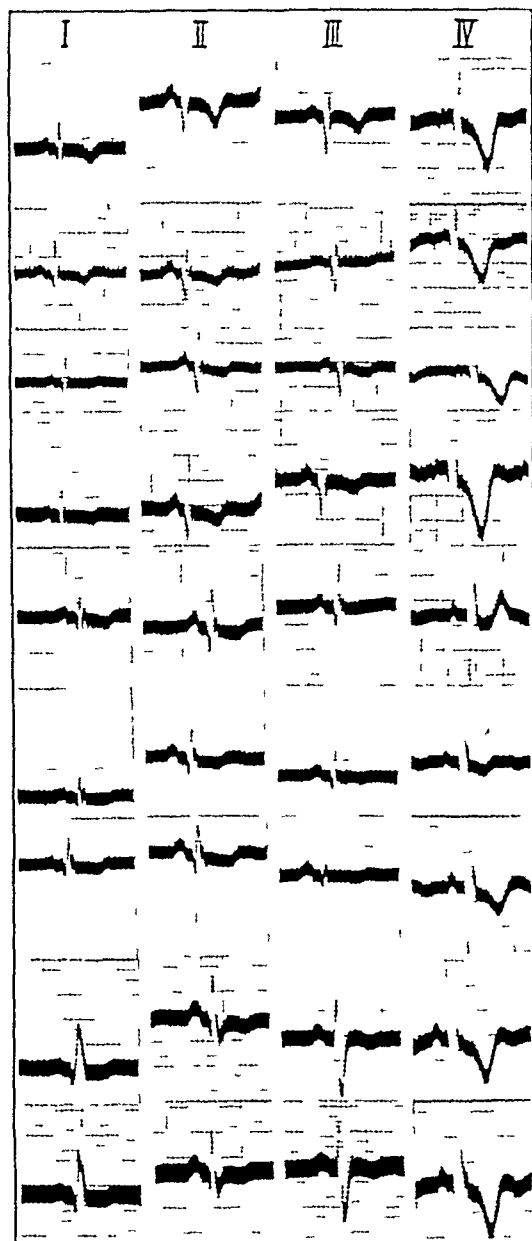


Fig 18—Serial electrocardiograms showing a late stage of atypical infarction of the posterior wall with a transitory change suggesting the superposition of infarction of the anterior wall, with recovery

Attack
Curves taken

6/29/33
7/21/33
8/17/33
9/22/33
1/24/34

Attack
Curves taken

6/20/34
7/3/34
8/9/34
9/12/34
1/15/35
2/29/35
6/1/35

Death (no autopsy)

In the group of cases of chronic coronary insufficiency, whether non-progressive or progressive, which we have previously reported¹¹ and to which we have now added 8 additional cases with autopsy data, some of the electrocardiograms resemble those encountered in cases of myocardial infarction (fig 10), except that the serial curves do not follow the course typical of cases of healing infarction. Others in this group show abnormalities of a more indeterminate nature (fig 9). There are a number of reports in the literature of similar cases²⁷. It is possible that the presence of electrocardiographic changes resembling those seen in cases of recent infarction is evidence of localized ischemia while absence of such changes is evidence of more generalized ischemia. It appears that the electrocardiogram not only does not depict the fibrosis or even the infarction but depicts only the presence of localized or gen-

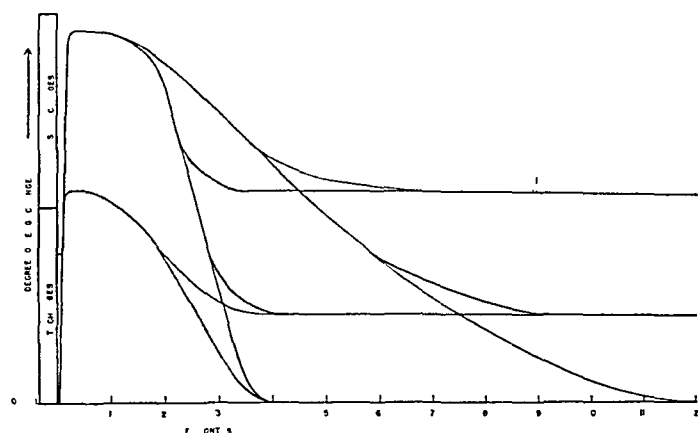


Fig 19—Diagram illustrating the possibilities of time events in a case of recent infarction as disclosed by serial electrocardiograms when at first there is little or no coronary insufficiency. The curves show (a) two degrees of severity of the attack, (b) two rates of recovery from the more severe attack, (c) complete and partial restoration and (d) (the dotted line) later superimposed acute transitory coronary insufficiency not giving rise to an infarct. When the patient starts with a certain degree of coronary insufficiency, as indicated by a short horizontal line half way up the upstroke, complete restitution will still leave an abnormal electrocardiogram.

eralized ischemia of the living muscle cells. This was the conclusion we came to in our previous study¹¹.

Transitory (acute) coronary insufficiency is another type of condition which is often noted in cases of coronary disease. It usually

²⁷ Burton, J. A. K., Cowan, J., Kay, J. H., Marshall, A. J., Rennie, J. K., Ramage, J. H., and Teacher, J. H. Four Cases of Fibrosis of the Myocardium with Electrocardiographic and Post-Mortem Examination, *Quart. J. Med.* **23**: 293, 1930. Levine and Brown⁷¹. Gilchrist and Ritchie⁷². Nathanson⁷⁰.

occurs²⁸ as the result of excessive effort an emotional crisis, very irregular or very rapid heart action or infarction of the kidneys spleen or lungs during congestive heart failure, or as the result of syphilitic involvement at the mouth of the coronary arteries. These conditions may produce transitory (acute) coronary insufficiency which does not result in permanent injury to the myocardium, although causing temporary electrocardiographic deformity and giving rise to such findings and symptoms as pulmonary edema cardiac asthma paroxysmal (nocturnal) dyspnea and angina pectoris. The occurrence of such changes in the electrocardiogram in the presence of these complications should make one seriously consider the transitory (acute) type of coronary insufficiency. The character of the electrocardiographic abnormalities associated with this condition will depend also on whether the process is diffuse or localized. Such transitory electrocardiographic changes again

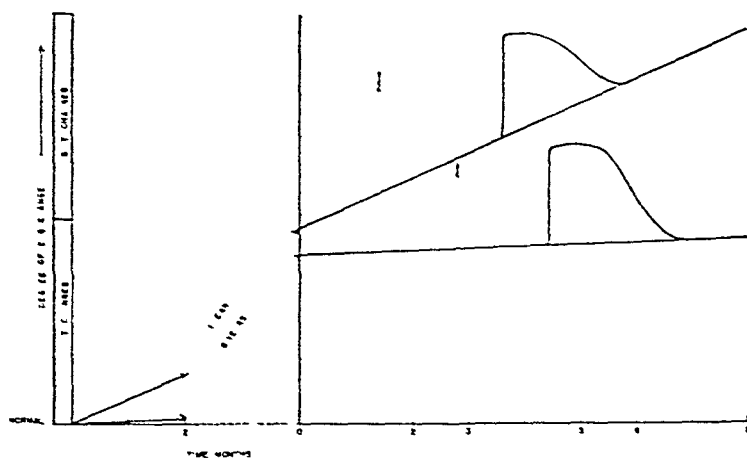


Fig. 20—Diagram illustrating the difference in time course between so-called nonprogressive (lower curve) and progressive (upper curve) chronic coronary insufficiency. On each of these curves is shown a superimposed curve for transitory coronary insufficiency (dotted lines) and a superimposed curve for a subacute attack with infarction (solid lines).

28 Katz, L. N., Hamburger, W. W., and Schutz, W. J. The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris. *Am Heart J* 9:771, 1934. Feil, H., and Siegel, M. L. Electrocardiographic Changes During Attacks of Angina Pectoris. *Am J M Sc* 175:255, 1928. Brow, G. R., and Holman, D. V. Electrocardiographic Study During a Paroxysm of Angina Pectoris. *Am Heart J* 9:259, 1933. Parkinson, John, and Bedford, D. E. Electrocardiographic Changes During Brief Attacks of Angina Pectoris. *Lancet* 1:15, 1931. Wood, F. C., and Wolferth, C. C. Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Occlusion. *Arch Int. Med* 47:339 (March) 1931. Hall, D. Electrocardiograms of Two Patients During Attacks of Angina Pectoris. *Lancet* 1:1254, 1932.

suggest that it is the ischemia of living muscle and not the presence of dead or scar tissue which causes the abnormalities observed with all forms of coronary insufficiency

GENERAL SUMMARY AND CONCLUSION

We have reported on 200 cases of coronary occlusion studied for three years. We have made a careful detailed analysis of the incidence of various abnormalities in the standard three leads and the deviations of lead IV in cases of (a) recent anterior infarction, (b) recent posterior infarction and (c) combined anterior and posterior infarctions. The criteria for this division according to the type of infarction were based on the characteristic electrocardiographic deviations in our own and in other cases in which the diagnosis was verified at autopsy.

We have presented illustrations of the four lead electrocardiograms in 25 cases of recent infarction together with the pertinent autopsy data. Similar data are presented for 2 cases of recent small multiple infarcts and for 8 cases of coronary sclerosis without infarction. We have illustrated with actual serial curves and with diagrams the evolution of the classical changes in cases of recent anterior and posterior infarction due to thrombosis.

We have demonstrated the differences in the electrocardiogram in cases of recent infarction due to suddenly occurring coronary thrombosis and in cases of infarction due to slowly occluding sclerotic plaques.

We have, as a result of these studies, reached the following conclusions:

The incidence of all types of myocardial infarction due to coronary occlusion is greater in men than in women, and the incidence of anterior infarction is greater than that of posterior infarction.

The mortality from posterior infarction is relatively less than that from other types.

Septal involvement occurs with all types of myocardial infarction but it is relatively more frequent with anterior infarction. If the septal infarction is near the apex, intraventricular block may not appear in the electrocardiogram.

Low "voltage" in the standard three leads occurs relatively more often with anterior infarction, but lead IV is usually not affected.

Preponderance of the left ventricle is most often associated with posterior infarction but may occur with anterior infarction.

Lead IV is of definite aid in the diagnosis of recent myocardial infarction due to coronary occlusion, especially anterior infarction.

The frequency of the various types of recent myocardial infarction is more in accord with autopsy statistics when four leads are used than when only the three limb leads are used.

Correlation with autopsy data shows

(a) The classic forms of electrocardiographic variation with early striking typical variations in the ST segment, are associated with recent infarction due to suddenly occurring thrombosis in a coronary artery

(b) Atypical forms of electrocardiographic variations are in most cases associated with recent infarction due to slowly occluding sclerotic plaques, with extensive coronary sclerosis, but they are also seen (1) in cases in which a recent infarction is superimposed on an old one (2) in the presence of recent multiple small infarcts or (3) in cases of recent infarction complicated by intraventricular block

(c) In the absence of infarction, chronic coronary insufficiency due to coronary sclerosis may result in an electrocardiogram resembling that typical in cases of coronary occlusion or one possessing noncharacteristic abnormalities associated usually with a QRS_1 which is mainly or entirely upright. Serial curves will easily differentiate the former condition from a healing recent infarction

(d) Transitory (acute) coronary insufficiency may produce electrocardiographic changes resembling those due to recent infarction without producing recognizable evidence of myocardial infarction post mortem. However, the rate of evolution in serial curves is different in the two conditions

(e) Myocardial infarcts do heal and may not leave any clearly demonstrable anatomic evidence, and serial electrocardiograms are therefore vital in the demonstration of this recovery

(f) In cases of chronic coronary insufficiency, progressive deviation from the normal in serial electrocardiograms is an unfavorable prognostic sign

Charts are given to depict the time course with the different types of coronary insufficiency, and a series of idealized records is shown to depict the classic series of changes in leads I, III and IV in a typical case of recent anterior and a typical case of recent posterior myocardial infarction

The manner of recording lead IV and the nomenclature to be used with respect to various kinds of chest leads are discussed

The importance of basing the final diagnosis on the findings in all four leads and on changes in serial curves rather than on any special abnormality in any single record is emphasized

NOTE.—The lead IV described in this report differs from the lead IV recently recommended by a special committee of the American Heart Association²⁹ as follows

1 The precordial electrode in our studies is placed in the fourth interspace just to the left of the sternum whereas for the standard lead

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IV recommended by the American Heart Association's committee the precordial electrode is placed over the apex

2 The electrodes in our studies are arranged so that relative positivity of the precordial electrode will cause a downward deflection, whereas according to the standard lead IV recommended by the American Heart Association's committee, the electrodes are arranged so that relative positivity of the precordial electrode gives an upward deflection

The medical staff of Michael Reese Hospital gave us permission to study their patients and cooperated in the obtaining of follow-up data, Dr O Saphir, of the Department of Pathology, supplied the autopsy reports, Miss Phillips and Miss Bronson, electrocardiographic technicians, and several interns were of technical assistance, and Mrs Salzman, social worker, assisted in obtaining the follow-up data for the clinic patients

FEVER INDUCED BY THE INTRAVENOUS INJECTION OF TYPHOID-PARATYPHOID VACCINE

S W RANSON JR, M D

NEW YORK

Since vaccines of the typhoid group are administered intravenously in arthritis, iritis, thrombo-angitis obliterans and other conditions and since there does not seem to have been any adequate study of the reaction caused by these vaccines, an inquiry into the more detailed nature of the normal response to the injection should serve a useful purpose. During a series of experiments designed to determine the effect of various hypothalamic lesions on the course of fever induced in cats by the intravenous injection of typhoid-paratyphoid vaccine, sixteen normal cats were studied.

Pinkston¹ recorded the inguinal temperature of twelve normal cats to which typhoid-paratyphoid vaccine had been administered intravenously. He made readings every 10 to 30 minutes "until the body temperature had started toward normal." Cannon and Pereira² described the temperature curves obtained for ten normal cats after intravenous or intramuscular injection of a suspension of dead typhoid bacilli. They did not state by what route the temperature was taken, nor did they describe the curves in any detail.

METHODS

Each cat was brought to the laboratory about 8 a. m., laid on its side on a specially designed canvas sling and secured in this position with canvas straps. It was thus securely but comfortably held.

The temperature was recorded in ink as a continuous curve by means of a Leeds and Northrup resistance temperature recorder, the resistance unit of which was inserted through the rectum and held securely in the colon at a constant distance of 14 cm. from the anus. A constant and deep placement of this unit was necessary because it was found that a temperature gradient exists in the cat's rectum between the outlet and a depth of from 8 to 10 cm. The resistance recorder was calibrated once a week against a United States Bureau of Standards thermometer in a constant temperature water bath. An area about

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This study was aided by grants from the Rockefeller Foundation and the Committee on Scientific Research of the American Medical Association.

1 Pinkston, J. O. Experimental Fever in Sympathectomized Animals, *Am J Physiol* **111** 539 (April) 1935.

2 Cannon, W. B., and Pereira, J. R. Increase of Adrenal Secretion in Fever, *Proc Nat Acad Sc* **10** 247, 1924.

3 or 4 cm in diameter on the side of the cat's flank had been depilated the preceding day, and to this area a skin thermocouple was applied by means of a spring-mounted holder fastened to a ring-stand. The room temperature and humidity were recorded at frequent intervals from a wet and dry bulb thermometer, ventilated at about 3 meters per second by an electric fan.³ All temperatures were recorded in degrees Fahrenheit.

In each case the animal was placed in the sling immediately on being brought to the room, and all the apparatus was mounted and placed in function. The temperature curve was then recorded until a definitely stabilized base line had been established. This precaution is of considerable importance, the process of stabilization may consume 2 or 3 hours. When the animal's temperature had been definitely stabilized, 0.35 cc of typhoid-paratyphoid vaccine⁴ per kilogram of body weight was injected into the saphenous vein. One uniform lot was used, all the vials having been filled at the same time from the same bottle of freshly prepared stock vaccine. The vaccine contained 1,000,000,000 killed typhoid, 750,000,000 killed paratyphoid alpha and 750,000,000 killed paratyphoid beta organisms in each cubic centimeter. The dosage was not varied at any time. Observations were made of the respiration and the skin temperature at frequent intervals (from 5 to 15 minutes) for 3 or 4 hours after the injection. It was not possible to make reliable observations on the pulse rate. About 5 p. m. the skin thermocouple was removed, the fan ventilating the wet bulb thermometer was stopped and the set-up was left otherwise undisturbed, so that a constant record of the animal's temperature was made until the termination of the experiment the next morning, about 20 hours after the injection.

RESULTS

Often immediately, almost always within from 10 to 30 minutes, after the injection the temperature began to rise, usually accompanied with or preceded by shivering. Generally the pupils were dilated, and the animal was excited and restless. On some occasions there appeared to be erection of hair. The skin thermocouple indicated cutaneous vasoconstriction. There was a moderate decrease in respiration. On an average of 48 minutes after injection of the vaccine the temperature reached a preliminary peak (hereafter called the first peak) at an average elevation of 1.2 F above the base line (chart 1). Three of the normal animals showed no definite first peak. Shivering now ceased or, more usually, had been absent for from 10 to 15 minutes before the attainment of the first peak. The pupils narrowed, in nearly every case defecatory movements began,⁵ usually with passage of considerable

3 The highest recorded room temperature was 83 F, the lowest, 76 F, the greatest variation during any one experiment, 2 F. The highest recorded relative humidity was 45 per cent, the lowest, 23 per cent, the greatest variation in relative humidity during any one experiment, 2 per cent.

4 The vaccine was furnished by the Abbott Laboratories.

5 It is realized that these movements were in part occasioned or exaggerated by the presence in the colon of the rectal resistance unit. Their significance lies in their constant temporal correlation with other events of a parasympathetic nature.

soft stool, occasionally with urination and, in the male, erection of the penis. Respiration was accelerated, and on three occasions the animal panted for from 5 to 15 seconds. The skin thermocouple indicated cutaneous vasodilatation. The rectal temperature fell away rapidly from the first peak to an average intermediate low point 0.6 F below the base line, reached on an average of 114 minutes after the injection. Only one animal showed no such definite intermediate fall. Shortly before the low point of this intermediate fall was reached, the animal usually began to shiver, the pupils dilated and respiration became slower. The skin thermocouple indicated cutaneous vasoconstriction. In the train of these symptoms the temperature again began to rise, not so steeply as during the first rise, but more sustainedly, attaining a peak (hereafter called the second peak), averaging 1.8 F above the base line, at an average of 279 minutes after the injection. Four of the

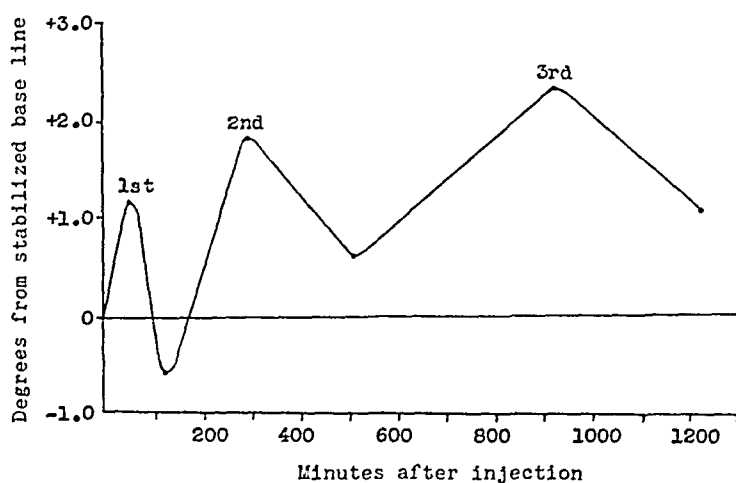


Chart 1—Composite temperature curve for sixteen normal cats after injection of typhoid-paratyphoid vaccine intravenously. On the ordinate is plotted the body temperature in degrees Fahrenheit above or below the stabilized preinjection temperature. Time in minutes is represented on the abscissa.

sixteen animals showed no well marked second peak. The temperature fell away from the second peak slowly and irregularly, with minor ups and downs, to reach on the average, a second intermediate low point, 0.57 F above the base line, 506 minutes after the injection. Then began a slow and irregular rise toward a third peak, which, on the average, reached 2.3 F above the base line 922 minutes after the injection. Thereafter the temperature fell slowly and irregularly. The next morning the temperature still averaged 1.06 F above the base line. Only two animals failed to show a reasonably well defined second intermediate fall and a third peak. Chart 2 shows a fairly typical temperature curve for a normal cat, but the fall after the first peak was smaller than usual.

One of the sixteen normal cats (experiment 22) responded to the injection in a peculiar manner. During the first 45 minutes after the injection the temperature remained practically constant, although the cat shivered once or twice. Thereafter the rectal temperature fell rapidly to a low point, 2.3 F below the base line, 209 minutes after the injection. From this point it rose, accompanied with some shivering, to a peak, 0.8 F below the base line, 378 minutes after the injection. After a minor recession from this peak it rose to a third peak, 0.4 F above the base line, 1,121 minutes after the injection. It fell away slowly from this point, until at the conclusion of the experiment, 1,275 minutes after the injection, the temperature was exactly at the base line. This cat was apparently perfectly normal and healthy. There had been no alteration in the conditions of the experiment.

The average respiratory rate of the stabilized animals just before the injection was 50.7 per minute. The average highest rate in the period between injection and attainment of the first peak was 46, the

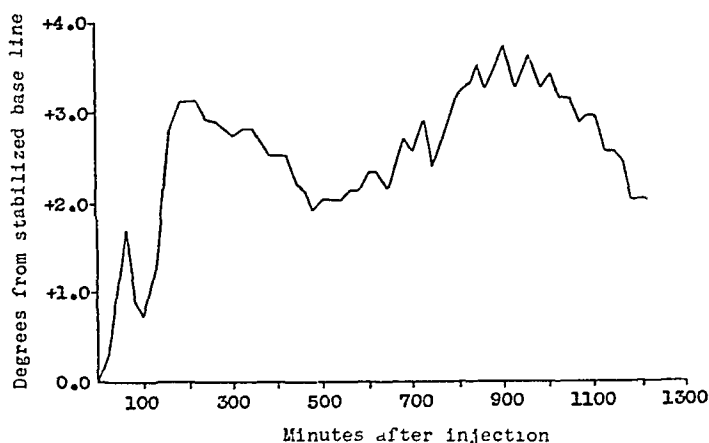


Chart 2—Typical temperature curve for the normal cat (experiment 25) after injection of typhoid-paratyphoid vaccine intravenously

average lowest rate for this period, 42.8. The average highest rate for the period between the first peak and the trough of the intermediate fall was 92.7, the average lowest rate for this period, 48. Three animals panted for from 5 to 15 seconds during this period, but the respiratory rate during panting, being of such short duration, was not entered on the charts or averaged into the respiratory rates of this period. Hence the averages are not unduly weighted by these occurrences. In the period of rising temperature between the trough of the intermediate fall and the second peak, the average maximum respiratory rate was 41.1 and the average minimum rate 33.1 per minute. There was thus some slowing of respiratory rate during the first rise, considerable acceleration during the intermediate fall and a return to a slow respiratory rate in the phase of the second rise.

All but two of the sixteen animals shivered during one or the other of the two phases of rising temperature. Nine shivered during the first rise, ten, during the second rise.

The readings for the skin thermocouple were of course not readings of true cutaneous temperature. Owing to the method of application of the thermocouple, there was present an unevaluated element of deep temperature, which would increase the reading of the skin thermocouple during a period of rising general body temperature and would therefore decrease the apparent amount of cutaneous vasoconstriction, during a period of falling general body temperature it would decrease the reading of the skin thermocouple and therefore would decrease the apparent amount of cutaneous vasodilatation. It is obvious, however, that if cutaneous vasoconstriction is indicated during a rise or fall in body temperature, it is undoubtedly present, although not accurately measured.

All but one of the thirteen animals that showed a definite first peak showed cutaneous vasoconstriction during that period, as judged by failure of the reading for the skin thermocouple to rise by the same amount as the rectal temperature. This lag averaged 0.4 F. All but two of the fifteen animals that exhibited a definite intermediate fall showed cutaneous vasodilatation, averaging 0.4 F, as calculated by this method. Six of the eight animals exhibiting a definite second peak, and for which the data were complete, showed cutaneous vasoconstriction, as judged by this method, the average being 0.3 F.

COMPARISON WITH THE RESULTS OF OTHER INVESTIGATORS

Cannon and Pereira² and Pinkston¹ described normal temperature curves after the injection of typhoid and of typhoid-paratyphoid vaccine respectively. Cannon and Pereira administered the vaccine either intramuscularly or intravenously and did not give any of the details of their experiment, i. e., method of taking temperature, method of stabilizing temperature before injection, dose of vaccine and interval between individual observations of temperature. Pinkston took the temperature inguinally instead of rectally, observations were spaced at intervals of from 10 to 30 minutes. He assumed stabilization of the preinjection body temperature after the animal had been in the laboratory 1 hour.

Both papers described first and second peaks with an intermediate fall. Neither paper described a third peak since both groups of experimenters apparently terminated their observations after the attainment of the second peak. Cannon and Pereira stated that the second peak may exceed the first. Pinkston stated that the first peak usually exceeds the second. I found that the second peak was almost always higher than the first, in contrast again to Pinkston's results. I found that in the fall from the first peak the temperature usually returned to the base line or below. I believe that the discrepancies between my results

and those of Pinkston may well be due to the errors which were inherent in his method of taking the temperature, i. e., originally, that method of observation is complicated by components of cutaneous vasoconstriction and vasodilatation. Cannon and Pereira found shivering in the first rise, but not in the second. I found it actually more common in the second than in the first. Cannon and Pereira mentioned the signs of sympathetic stimulation during the rise toward the first peak, and these were also briefly touched on by Pinkston. Neither paper mentioned parasympathetic symptoms during the period of falling temperature.

CONTROL EXPERIMENTS

In order to determine what range of variation in temperature might be expected in the cat merely as the result of the normal diurnal variation, together with the manipulation to which the animals were subjected during these experiments, two normal cats were carried through exactly the same procedure as were the main series of sixteen cats, except that instead of typhoid-paratyphoid vaccine an equal volume of sterile physiologic solution of sodium chloride was injected intravenously. The first of these control animals showed a highest upward variation from the stabilized base line of 0.9 F. The lowest downward variation from the base line was 0.2 F. The second cat showed a highest upward variation from the base line of 0.3 F. The lowest downward variation was 0.7 F.

The range of total variation was 1.1 F for the first cat and 1 F for the second cat. This corresponds well with the normal diurnal variation of temperature in the cat reported by Pinkston as from 0.9 to 1.8 F. It is apparent that the manipulations of the experiment had little if any effect.

To make certain that the effects described in the main body of the experiment were not merely those of a particular brand or shipment of typhoid-paratyphoid vaccine and, further, to make certain that they were not properties of a mixed vaccine that would not be found in a vaccine prepared from typhoid bacilli alone, a sample of unmixed typhoid vaccine was obtained from the Chicago Board of Health. A dose of this vaccine, which contained a number of organisms equal to that used in the main experiment on the series of sixteen cats, was injected intravenously into each of two normal cats. The resultant temperature curves and other observations differed in no essential detail from the norms established by the other experiments. The detailed data will not be given.

Effects of Ether.—In addition, five normal animals were anesthetized as a preliminary with ether by inhalation for about 10 minutes. While each animal was in a stage of light surgical anesthesia, the usual dose of typhoid-paratyphoid vaccine was injected intravenously, and the anesthetic was at once discontinued. All other conditions were similar to those in the typical experiments. After the injection two of the animals showed an almost immediate fall in temperature, accompanied with pupillary constriction, excessive salivation, marked defecatory movements and marked and persistent panting. The temperature of one of the animals dropped 5.9 F and that of the other 4.2 F. The experiment on the first animal was terminated the same day, the second was followed for 20 hours, and at the end of that time the temperature was still 4.2 F below the base line. In the other three animals the first peak was lowered or absent, and panting, salivation, defecation and pupillary constriction were marked. Eventually, however, the temperature rose to a point well above the base line (4.3, 4 and 3.2 F, respectively).

COMMENT

The normal process of conservation of bodily heat apparently entails, among other mechanisms, mass sympathetic stimulation. Cannon and Querido⁶ demonstrated that an animal with a denervated heart shows marked acceleration in cardiac rate when exposed to cold, this they said is indicative of increased secretion of epinephrine. According to Aub, Bright and Forman,⁷ McIver and Bright⁸ and Cori and Buchwald,⁹ the liberation of epinephrine increases the oxidative processes of the body. Sympathectomized animals are more susceptible to cold than are normal animals, and they lose their body heat more rapidly when exposed to it (Cannon, Newton, Bright, Menkin and Moore,¹⁰ Sawyer and Schlossberg¹¹).

H. H. Meyer¹² advanced the theory that the mechanism for regulation of body temperature includes two centers, one of which, promoting increases in temperature, gives rise to generalized sympathetic reactions, and the other, promoting decreases in temperature, causes generalized parasympathetic reactions. Phenomena present in normal cats during the phases of rising temperature (excitement, dilatation of the pupils, cutaneous vasoconstriction and occasionally erection of hair) suggest a state of generalized sympathetic stimulation. Similarly those phenomena which accompany the phases of falling temperature (pupillary constriction, cutaneous vasodilatation and defecation and occasionally urination and penile erection) suggest a period of generalized parasympathetic stimulation.

It is well known that drugs which stimulate the sympathetic system, such as epinephrine, tyramine hydrochloride and other amines, ephedrine and especially betatetrahydronaphthylamine, all produce fever if given in sufficient doses. Pinkston¹ found that completely sympathectomized

6 Cannon, W. B., and Querido, A. The Role of Adrenal Secretion in the Chemical Control of Body Temperature, *Proc. Nat. Acad. Sci.* **10** 245, 1924.

7 Aub, J. C., Bright, E. M., and Forman, J. The Metabolic Effect of Adrenalectomy upon the Urethanized Cat, *Am. J. Physiol.* **61** 349 (July) 1922.

8 McIver, M. A., and Bright, E. M. Changes in Metabolism Following Adrenal Stimulation, *Am. J. Physiol.* **68** 622 (May) 1924.

9 Cori, C. F., and Buchwald, K. W. The Calorigenic Action of Epinephrine in Frogs Before and After Hepatectomy, *J. Biol. Chem.* **92** 367 (July) 1931.

10 Cannon, W. B., Newton, H. F., Bright, E. M., Menkin, V., and Moore, R. M. Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, *Am. J. Physiol.* **89** 84 (June) 1929.

11 Sawyer, M. E. M., and Schlossberg, T. Studies of Homeostasis in Normal, Sympathectomized and Ergotaminized Animals. I. The Effect of High and Low Temperatures. *Am. J. Physiol.* **104** 172 (April) 1933.

12 Meyer, H. H. Theorie des Fiebers und seiner Behandlung. *Verhandl. d. deutsch. Kongr. f. inn. med.* **30** 15, 1913.

animals to which typhoid-paratyphoid vaccine was administered intravenously displayed a slow rise to a late and low maximum temperature, with an absence of conspicuous peaks. Animals subjected to the same type of injection, in which only the splanchnic sympathetic outflow was intact, showed a similar response, although the maximal temperature occurred earlier and distinct peaks were more common. Cannon and Perena² found that the first temperature peak induced in normal animals by the injection of typhoid vaccine did not occur after inactivation of the adrenal glands. Pinkston, on the other hand, found that when the only lesion of the sympathetic nervous system was inactivation of the adrenal glands there were usually two distinct temperature peaks. In these animals the speed of attainment of maximal fever was almost, but not quite, that of normal animals.

G. E. Brown and his associates,¹³ wishing to determine the amount of vasodilatation available in an extremity affected by thrombo-angitis obliterans, followed the simultaneous courses of oral and cutaneous temperatures after the injection of typhoid vaccine intravenously into patients afflicted with this disease. During the course of the ensuing chill (period of rising general body temperature) there was a marked fall in the cutaneous temperature of the extremity. At, or just before, the peak of this rise there was tremendous vasodilatation, and the cutaneous temperature of the extremity rose well above the base line originally established. The absolute rise in cutaneous temperature was much greater than the absolute rise in oral temperature. Accompanied with this vasodilatation, the oral temperature fell away from the peak (The authors did not follow the course of events beyond this point). Thus, in the human being, as in normal cats, the period of rising temperature is accompanied with vasoconstriction, the period of falling temperature, by vasodilatation.

Pinkston¹⁴ noted prompt vasoconstriction, with a fall in cutaneous temperature, in the ear of the normal rabbit after injection of typhoid-paratyphoid vaccine. This appeared within a short time (5 to 10 minutes) after the injection and persisted until the peak of the temperature had been reached, to be replaced suddenly by a rise in cutaneous temperature (vasodilatation). The body temperature then fell. The course of events was not followed beyond this point. There was some vasoconstriction (but only in 50 per cent of the cases) in the sympathectomized ear. Inactivation of the adrenal glands appeared to do away

13 Brown, G. E., Allen, E. V., and Mahorner, H. R. *Thrombo-Angitis Obliterans*. Philadelphia, W. B. Saunders Company, 1928, p. 182. Brown, G. E. *Thrombo-Angitis Obliterans*, *Surg., Gynec. & Obst.* **58**: 297 (Feb.) 1934.

14 Pinkston, J. O. *Peripheral Circulation During Experimental Fever*, *Am. J. Physiol.* **110**: 448 (Dec.) 1934.

with the early vasoconstriction in the sympathectomized cat, but had no effect on the delayed vasoconstriction (that appearing after from 1 to 3 hours)

Hewlett¹⁵ studied the rate of blood flow in the periphery in several cases of abrupt febrile rises due to sepsis in the human being. There was a decrease in the rate of flow during the period of rising temperature. When the temperature reached its peak there was a marked increase in flow, exceeding the original rate of flow and persisting on into the period of falling temperature.

Fremont-Smith, Morrison and Makepeace¹⁶ made direct microscopic observations of the capillaries of the human nail fold during the febrile reaction produced by the injection of typhoid vaccine. They found that, coincident with the onset of the fever, complete capillary stasis occurred rapidly, the stasis continuing until the temperature had nearly reached its height. Just before the height of the temperature was reached the flow of blood again began in the capillaries, rapidly reaching a more than normal rapidity. Capillary pulsation set in. The temperature simultaneously began to fall. The rapid flow lasted throughout the period of falling temperature. The authors said that they believed that the stasis during the period of rising temperature is due to constriction of the terminal arterioles.

To summarize. The febrile process induced by the intravenous injection of typhoid-paratyphoid vaccine seems to consist of alternate stimulation of the mechanism for conservation of bodily heat, *including the sympathetic system*, and then of the mechanism for loss of bodily heat, *including the parasympathetic system*. Probably the two antagonistic mechanisms are stimulated simultaneously, first one and then the other predominating. The cycle of these alternate reactions is apparently repeated at least several times, and the algebraic result in the normal animal when this particular bacterial protein is used is a period of many hours in which the body temperature, although rising and falling in cycles, is maintained at some distance above the base line.

Not all vaccines when injected into animals cause sustained fever. Pfeiffer¹⁷ showed that chloroform-killed cholera vaccines when injected intraperitoneally drove the animal's temperature down to 33 C., with signs of collapse. After small doses there was merely a slight rise in

15 Hewlett, A. W. The Effect of Room Temperature upon the Blood-Flow in the Arm, with a Few Observations on the Effect of Fever, *Heart* 2:230, 1911.

16 Fremont-Smith, F., Morrison, L. R., and Makepeace, A. W. Capillary Blood Flow in Man During Fever, *J. Clin. Investigation* 7:489 (Aug.) 1929.

17 Pfeiffer, R. Untersuchungen über das Choleragift, *Ztschr. f. Hyg. u. Infektionskr.* 11:393, 1892. Pfeiffer, R., and Wassermann, A. Untersuchungen über das Wesen der Choleraimmunität, *ibid.* 14:46, 1893. Pfeiffer, R. Studien zur Choleraätiologie, *ibid.* 16:268, 1894.

temperature After larger doses there was a slight rise in temperature, then in 2 or 3 hours, marked hypothermia Novy, De Kruijff and Novy,¹⁸ among others, stated that when autolyzed suspensions of *Trypanosoma surra*, *nagana* and others are injected there occur "marked toxic effects," with hypothermia

One is tempted to assume that various bacterial proteins may differ in their proportionate effects on the mechanisms of heat preservation and heat loss and that the algebraic summation of the cyclic action of these mechanisms results in hyperthermia in the normal animal with the usual bacterial proteins, but causes hypothermia in the normal animal when cholera and trypanosome vaccines are used

Further, it may be assumed that if the mechanism of heat preservation or of heat loss or the mechanism coordinating them is abnormal injection of the usual bacterial proteins may produce hypothermia in animals possessing the abnormal mechanism, although the protein injected is one that ordinarily produces a hyperthermic response Thus, mere preliminary etherization of the animal for from 5 to 10 minutes is often sufficient to render its response so abnormal that hypothermia results from the injection of typhoid-paratyphoid vaccine, in spite of the fact that etherization of that duration will not of itself produce any noteworthy fall in temperature Much more striking were the results obtained by injection of typhoid-paratyphoid vaccine intravenously into cats with certain hypothalamic lesions The cats responded in a cyclic manner, but the falls in temperature much exceeded in magnitude the rises, the final algebraic result being sustained and tremendous hypothermia (5 to 11 F) (These results will be published in detail in a separate paper)

The infrequent fatal and near fatal reactions which have occurred as a result of the injection of typhoid vaccine by the various routes have not been adequately described or explained Reported during these reactions have been dyspnea and cyanosis (Nichols and Hitchens¹⁹), vomiting and marked fall in blood pressure (Scully²⁰), and dyspnea, cyanosis and dilatation of the heart (Hale and Hartman²¹) In none of these cases were records of the temperature made until there was marked improvement in the patient's condition Some of these violent reactions are reminiscent of the parasympathetic symptoms attendant on the

18 Novy, F G, De Kruijff, P H, and Novy, R L Anaphylatoxin and Anaphylaxis, *J Infect Dis* **20** 499, 535, 566, 589, 618, 629, 657 and 776, 1917

19 Nichols, H J, and Hitchens, A P The Reactions of Typhoid Vaccination, *J Lab & Clin Med* **11** 517 (March) 1926

20 Scully, F J The Reactions After Intravenous Injections of Foreign Protein, *J A M A* **69** 20 (July 7) 1917

21 Hale, G D, and Hartman, F W The Dangers of Intravenous Injection of Anti-Typhoid Vaccine, *U S Nav M Bull* **12** 1 (Jan) 1918

phases of falling temperature in the cats in the experiments reported here, especially in the abnormal animals in which hypothermic and parasympathetic reactions predominated

There seems to be general agreement that epinephrine is the treatment of choice in these accidents and that its administration is actually followed by amelioration of the symptoms (Nichols and Hitchens¹⁹ and Hench²²) Hench also mentioned the use of atropine in these situations The reactions have been regarded by many as expressions of anaphylaxis (among others, Hale and Hartman²¹ and Nichols and Hitchens¹⁹), but this view is by no means universally held (Miller²)

From 1914 to 1920 there was considerable interest in the treatment of typhoid by the intravenous injection of typhoid vaccine The results were striking From half an hour to an hour after the injection there occurred a chill, lasting for from 10 to 20 minutes, the temperature rising to 40 or 41 C and then *falling sharply to normal or well below*, usually with marked sweating, often nausea and vomiting, and profuse liquid diarrhea in cases in which constipation had previously been present (among others may be cited Leschke,²⁴ Sladek and Kotlowski,²⁵ Eggerth,²⁶ Kraus²⁷ and Von Adelung²⁸) That this striking temperature reaction was not anaphylactic was shown by Kraus,²⁹ for intravenous injection of *Bacillus coli* vaccine in cases of typhoid produced similar results in his experience Indeed, so did intravenous injections of deuterio-albumose (Ludke³⁰) It may be assumed in the light of the foregoing discussion that the injection of vaccine intravenously into patients with typhoid produces after a preliminary rise in temperature, with predominance of the heat retention mechanism and sympathetic

22 Hench, P S Usual and Unusual Reactions to Protein (Fever) Therapy, *Arch Int Med* **49** 1 (Jan) 1932

23 Miller, J L The Non-Specific Character of Vaccine Therapy, *J A M A* **69** 765 (Sept 8) 1917

24 Leschke, E Erfahrungen uber die Behandlung der Kriegsseuchen, *Berl klin Wchnschr* **52** 634, 1915

25 Sladek, J, and Kotlowski, S Zur Vakzinetherapie des Typhus abdominalis *Wien klin Wchnschr* **28** 389, 1915

26 Eggerth, H Ueber die Behandlung des Typhus abdominalis mit Typhusvakzine, *Wien klin Wchnschr* **28** 209, 1915

27 Kraus, R Bemerkungen uber Schutzimpfungen und eine Bakteriotherapie des Typhus abdominalis *Wien klin Wchnschr* **27** 1443 (Nov) 1914

28 Von Adelung, E Vaccine Treatment of Typhoid, *California State J Med* **18** 175 (May) 1920

29 Kraus, R Zur Frage der Vakzinetherapie des Typhus abdominalis, *Deutsche med Wchnschr* **40** 1556, 1914

30 Ludke, H Die Behandlung des Abdominaltyphus mit intravenosen Injektionen von Albumosen, *Munchen med Wchnschr* **62** 321 (March) 1915

stimulation, the usual cyclic shift to predominance of the heat loss mechanism, with parasympathetic signs, but this phase of the cycle, for reasons which are not obvious, is markedly exaggerated and prolonged

SUMMARY

Typhoid-paratyphoid vaccine was injected intravenously into sixteen normal cats. The resultant temperature curves were recorded continuously for 20 hours. The reaction in the normal cat to the injection of typhoid-paratyphoid vaccine intravenously, which is described in detail, consists essentially of cyclic stimulation, first of the heat elaboration mechanism, with sympathetic signs, and then of the heat loss mechanism, with parasympathetic signs. The heat preservation mechanism predominates, so that the algebraic result is hyperthermia of a sustained nature. There are usually three temperature peaks, the third one being higher than the second and the second being higher than the first.

When the mechanism of heat preservation or of heat loss, or the mechanism coordinating them, is abnormal, the reaction to the injection of the vaccine may be one in which the heat loss mechanism, with parasympathetic signs, predominates, and the algebraic result may be marked and sustained *hypothermia*, although the bacterial protein is one which ordinarily produces hyperthermia. This abnormality of the mechanism of the animal which has been given an injection of vaccine may result from preliminary etherization or from localized lesions of the hypothalamus.

Certain bacterial proteins apparently differ from the usual bacterial proteins in that when injected into the *normal* animal they produce a cyclic response in which the heat loss mechanism, with parasympathetic signs, predominates, and the result is sustained and marked *hypothermia*.

Violent clinical reactions to the injection of typhoid vaccine and the remarkable thermolytic response which have been obtained by the intravenous injection of typhoid vaccine during the course of typhoid are considered in the light of the preceding discussion.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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I DISEASES OF METABOLISM

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DISORDERS OF FAT METABOLISM

Cholesterol Metabolism—Dis Thannhauser and Magendantz¹ have given me permission to include in this section the following review of a paper of theirs to be published in the near future. Dr Thannhauser and his associates are recognized as outstanding authorities on cholesterol metabolism, a subject which only recently, and to a great extent through their efforts, has become somewhat understandable. It now is well established that the nucleus of the sterols can be manufactured in the body although it remains not definitely known in what cells or organs this synthesis is accomplished. It is suspected that it is accomplished in the liver, at least the value for cholesterol in the blood is lowered by hepatectomy. Nor is there knowledge as yet as to what raw material serves as the source of the sterol skeleton, other than that certain yeasts are able to make ergosterol from various sugars—best from polysaccharides. Balance experiments with cholesterol are of little help in deciding whether the ring system of cholesterol can be disrupted in intermediary metabolism, for the reason that excretion occurs into the bowel and destruction of cholesterol can be effected there by bacteria. Disintegration products of the sterols, in which the sterol ring skeleton is broken up, have not been found in the blood or tissues, although derivatives dependent on changes in the side chain like the sex hormones are well known.

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¹ Thannhauser, S I, and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of Twenty-Two Cases, to be published.

The esterification of cholesterol occurs in the liver, if one may judge from the fact that that part of the value for the total cholesterol of the blood attributable to cholesterol esters frequently is diminished in disease of the parenchyma of the liver. Reduction (hydrogenation¹) to dihydrocholesterol can occur, as was reported by Schoenheimer and Hrdina,² who demonstrated dihydrocholesterol in the serum and tissues of normal men and increased amounts of it in the serum and tissues of a patient with xanthomatosis. However, the bile acids, which it was supposed might be derived from a stereo-isomer of dihydrocholesterol and thus from the sterols of the food, apparently are not so derived but originate by synthesis in the liver. It was found by Schoenheimer and his co-workers that when deuterium was attached to the double bond of cholesterol and this deuterium cholesterol was fed to animals, the bile acids afterward contained no deuterium.

The ability of the intestine to excrete cholesterol varies with the species, in man, according to Schoenheimer, there is variability with the individual. Herbivorous animals, while capable of absorbing it, cannot excrete it, which may explain the ease with which hypercholesteremia, with consequent atheromatosis, is obtained by feeding cholesterol to rabbits. The phytosterols of plants are not absorbed by either herbivores or carnivores, the possibility of favorably affecting conditions of hypercholesteremia in man by omitting animal fats from the diet was suggested thereby.

An important function of cholesterol is indicated "by the fact that cholesterol and cholesterol esters are present in a constant percentage in every lipid mixture occurring on the surface or within the cell."³ Cholesterol is a hydrophobic colloid and thus plays a part in the exchange not only of fat-soluble material but also of fluid. The presence in the tissues of dihydrocholesterol suggested to Thannhauser and Magendantz another function—a role in an oxidation-reduction system (cholesterol \rightleftharpoons dihydrocholesterol).

Hypercholesteremia may be taken to indicate that the excretion of cholesterol is not in pace with the supply, whether endogenous or exogenous. Its occurrence usually is associated with that of cells filled with lipids, called foam cells or xanthoma cells. Such cells are found in widely scattered nests in various organs or accumulated in tumorous masses, called xanthomas, in the skin and other tissues. However, as

2 Schoenheimer and Hrdina, cited by Thannhauser and Magendantz¹

3 I am not familiar with the evidence which supports this statement. The percentage of total lipid represented by cholesterol and cholesterol esters, as determined by chemical analyses of blood and xanthoma tissue, varies greatly (see Montgomery and Osterberg⁴)

Thannhauser and Magendantz have related conditions in which foam cells and xanthomas occur are not always dependent on an excess in the blood of cholesterol or other lipids

Xanthomatosis—The xanthomatoses have been classified by Thannhauser and Magendantz as primary and secondary. The secondary type they have attributed to hyperlipemia. Characteristic of it is the "eruptive" xanthomatosis of diabetes. The primary type they have subdivided into conditions characterized by elevated values for blood cholesterol and conditions characterized by normal values for the cholesterol and other lipids of the blood. The occurrence of xanthomatosis without hyperlipemia led them to depart from the view of Pick, that the xanthoma cell is simply a reticular cell overloaded with lipids as a result of hyperlipemia depending on some (unestablished) extracellular general disturbance of fat metabolism, and to suggest that the disturbance in question is intracellular and limited to certain reticular cells. They concluded that in those cases in which they classified the condition as primary or essential xanthomatosis, the xanthoma cells themselves form the doubly refractile substance they contain. They have pointed to analogies in other diseases of lipid metabolism as follows. In Gaucher's disease similar foam cells contain cerebroside, whereas the blood contains only traces of cerebroside. Likewise, in Niemann-Pick disease the content of the foam cells consists of diaminophosphatides (sphingomyelins), whereas the values of the blood serum for mono-aminophosphatides and diaminophosphatides are normal or even lower than normal. Further to emphasize this point of view, Thannhauser and Magendantz have suggested the term metaplastic reticular cholesterosis for essential xanthomatosis, metaplastic reticular cerebrosidosis for Gaucher's disease and metaplastic reticular sphingomyelinosis for Niemann-Pick disease.

Primary xanthomatosis, "a systemic disease," may be complicated by an eruptive xanthomatosis secondary to hyperlipemia. The eruptive form is a symptom of lipemia, and, in addition to occurring in diabetic lipemia may be seen in other states of hyperlipemia such as xanthomatous biliary cirrhosis wherein lipemia is produced and eruptive xanthomas are added to those previously existent.

The two types of primary or essential xanthomatosis, that with and that without hypercholesteremia, differ in other characteristics. In type A the lesion of the skin is either the xanthoma planum or the xanthoma tuberosum, with it occur xanthomas of the tendons and tendon sheaths of the blood vessels and of the walls of the bile ducts (with secondary biliary cirrhosis). In type B (without hypercholesteremia) the lesion of the skin is the xanthoma disseminatum, the pituitary body and the brain may be involved, and xanthomatous nodules may form in the membranous bones and in the orbit provoking the

Hand-Schuller-Christian syndrome. However, other bones, including the long bones, may be affected and also the lungs and the pleura. The two types of primary xanthomatosis are not rigidly distinct, as is indicated by the necessity for adding a "combined type" to the classification. Thannhauser and Magendantz have classified the condition in 3 cases reported in the literature as of this combined type.

Another extensive discussion of xanthomatosis is contained in a paper by Montgomery and Osterberg,⁴ whose comments likewise have been based on a study of a large number of cases. The most common form of cutaneous xanthoma, known as xanthoma tuberosum, was found almost invariably to be associated with an increase in the values for all the lipids of the blood, including cholesterol, of from two to five times the normal values. Also associated in a high percentage of cases was evidence of atheromatous lesions of the arteries. Thus, in 6 cases the clinical findings suggested the presence of coronary sclerosis, in 3 additional cases intermittent claudication was observed, and in 3 more there was other evidence of severe cardiovascular involvement. Three of the 4 patients with intermittent claudication (none of whom were Jews) and 3 of the patients with evidence of coronary sclerosis were women, which fact, combined with the early age of these patients—46 years—suggests that this form of atherosclerosis differs in etiology from the more common types of atherosclerosis and arteriosclerosis. Forty-six per cent of the group of 26 patients with xanthoma tuberosum had severe cardiovascular disease. Barker,⁵ in 2 of these cases, made special studies and convinced himself of the presence of severe occlusive arterial disease. The values for blood cholesterol exceeded 600 mg per hundred cubic centimeters, which is more than double the highest value for cholesterol found by him in a series of cases of the usual form of arteriosclerosis obliterans.

Disseminate xanthomatosis, represented by 4 of the cases of Montgomery and Osterberg, is characterized by multiple fine papular lesions of the skin of the flexural surfaces of the arms and frequently of the face. The mouth, pharynx and larynx also may be involved. Laryngeal obstruction necessitated tracheotomy in 2 of these cases. Mild diabetes insipidus also was present in 3 cases, and in 1 deposits of foam cells and deposits of cholesterol were seen at necropsy in the hypophysis and tuber cinereum. In contrast to the values in cases of xanthoma tubero-

4 Montgomery, Hamilton, and Osterberg. A. E. Xanthomatosis. Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, *Arch. Dermat. & Syph.*, to be published, Xanthomatosis. A Systemic Disease, *Proc. Staff Meet., Mayo Clin.* **12**: 641-644 (Oct. 13) 1937.

5 Barker, N. W. Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, paper read before the Central Society for Clinical Research, Chicago, Nov. 5, 1937.

sum, the values for the lipids in the serum were normal or subnormal. In many of the cases of xanthoma tuberosum the hyperlipemia could be corrected, and partial or complete involution of the cutaneous lesions could be effected by means of a diet low in fat or free from cholesterol (free from animal fat). In contrast, in the cases of disseminate xanthomatosis the cutaneous lesions could not be influenced by these dietary procedures. On the other hand, the histologic appearance of the tuberculous and that of the disseminate form of xanthoma were identical, revealing numerous foam cells and so-called Touton giant cells laden with lipids, the chemical analysis of lesions of both types revealed a "definite proportionate increase in the cholesterol content, reaching as high as 64 per cent of the total lipids and dropping to 18 per cent only in one old fibrous nodule which histologically revealed very few foam cells." This cholesterol content is much greater than that found in normal epidermis, and in 6 of 7 cases it exceeded the normal percentage ratio found for the lipids of the blood.

The lesion of the skin of the eyelids known as xanthelasma commonly has been regarded as having no serious significance. That this opinion may be erroneous and that xanthoma palpebrarum also may represent a metabolic disease were suggested. This condition frequently was seen in association with other forms of xanthoma of the skin, the histologic picture was found to be similar to that of other forms of xanthoma, and even in cases in which the only lesion of the skin was xanthelasma the values for serum lipids frequently were abnormally high.

Montgomery and Osterberg stated that they did not share Thannhauser's opinion that the cholesterol in the xanthoma is produced *in situ*. They said it did not seem logical to them to explain the hyperlipemia and hypercholesteremia in cases of xanthoma tuberosum by the production of lipids in the relatively few cutaneous nodules seen, and while the absence of increased values for blood lipids in cases of disseminate xanthomatosis might be explained by abnormal storage, the existence of such cases they regarded as opposed to the theory. Furthermore, there are numerous cases in which hyperlipemia has not been associated with cutaneous xanthomas. One of these was reported from the Mayo Clinic by Ochsner and Connor.⁶ The patient was a woman 55 years of age. She had been ill for less than two years with cardiac episodes and moderate elevation of the blood pressure. The blood was milky, and examination revealed values for total lipids, total fatty acids and cholesterol of 2,638, 1971 and 667 mg, respectively, per hundred

6 Ochsner, H. C., and Connor, H. M. Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease. Report of a Case and Partial Review of the Literature. *Ann Int Med* **10** 258-269 (Aug.) 1936.

cubic centimeters Six months later an attack of coronary disease proved fatal, the necropsy revealing as the only abnormality an extreme degree of atherosclerosis of the arteries The liver weighed 1,983 Gm It was only moderately infiltrated with fat and otherwise was not abnormal So far as could be determined this patient had always had a well rounded dietary, not unusually rich in fat or cholesterol The elevation of the lipid content seemed, therefore, to be on the basis of an anomaly of lipid metabolism, and the authors postulated that this was primary and the atherosclerosis secondary The alternate supposition, that the atheromatous lesions in the arteries were primary and the lipemia was attributable to rupture of atheromatous "abscesses," seems improbable However, it is possible that atherosclerosis such as this represents xanthomatosis limited to the arteries

For many years patients with epilepsy have been treated at the Mayo Clinic with the so-called ketogenic diet, in which the content of carbohydrate usually is less than 25 Gm, that of protein not more than 60 Gm and that of fat, depending on the total number of calories required by the patient, varying up to more than 200 Gm Such symptoms as those complained of by the patient of Ochsner and Conner have never been encountered in these patients However, in 2 children who died of other causes small atheromatous plaques were seen in the arteries The value for lipids in the blood of patients on the ketogenic diet is almost never abnormally high, but recently my colleagues and I have had experience with a case in which there developed an atypical form of eruptive xanthomatous lesion of the skin associated with hyperlipemia When the ketogenic diet was discontinued, the abnormality disappeared

It is my guess from the evidence presented and from other experience that cholesterol production is a function of reticulo-endothelial cells wherever located, that a second function of these cells is to remove cholesterol and other lipids from the blood when the level exceeds what is physiologic, and that in xanthomatosis and possibly also in atherosclerosis some of these cells, because of biologic inferiority, become incapable of disposing of the cholesterol they themselves have made (xanthomatosis without hyperlipemia) or have absorbed from the blood stream (xanthomatosis with hyperlipemia) and thereby take on the appearance of foam cells The cause of the hyperlipemia may be either an increased rate of synthesis of cholesterol by abnormal reticulo-endothelial cells or a high intake of cholesterol by persons who are incapable of maintaining a normal rate of excretion of cholesterol (Schoenheimer and Hrdina)

Treatment of Cholesterosis—Little is known about the treatment of conditions associated with excessive accumulation of cholesterol A

diet restricted in animal fat is sometimes effective, as has previously been stated. Exposure to roentgen rays is said to be of some effectiveness in xanthomatosis of the type not associated with hyperlipemia and in recent years a number of writers have affirmed that iodine in large doses inhibited the atheromatosis produced in rabbits by feeding them cholesterol. Thiersch,⁷ of the pathological institute in Freiburg has commented on this and has also presented the results of experiments on rabbits with a preparation of a pure extract of garlic, in combination with deoxycholeic acid. Garlic, it seems, is an old "folk remedy" for arteriosclerosis. A dose representing 5 Gm daily of garlic root was given to 33 animals, together with 0.3 Gm daily of cholesterol for ninety days. Eleven controls received only the cholesterol. At the end of the trial period the aorta and blood were analyzed for cholesterol. The average values for the rabbits receiving cholesterol and garlic were 185 and 405 mg per hundred cubic centimeters, respectively. Those for the rabbits receiving only the cholesterol were 543 and 641 mg respectively.

Xanthomatosis and Hyperlipemia in Diabetes—In a case reported by Nicholson⁸ under the title "Xanthoma Diabeticorum" there were many of the characteristics of the Cushing syndrome. At the age of 21 years the patient gained 80 pounds (36 Kg) in four months, showed purplish striations of the skin and had weekly headache in both temporal regions. He had held this weight twenty years, and five weeks before examination noticed a papular xanthomatous eruption affecting the entire body except the face. Hypertension, polycythemia, hyperglycemia (207 mg of sugar per hundred cubic centimeters) and glycosuria were found. There was no acidosis, and the diabetes was so mild that it was controlled without difficulty by a restricted diet and 15 units of insulin. The cholesterol content (total) at the first examination was 543 mg per hundred cubic centimeters. After four months, the diet having been restricted rigidly as to fat, the cholesterol content (total) had fallen to 262 mg. The ester fraction was high, and no evidence of hepatic disease was obtained. I wonder whether the term xanthoma diabeticorum should be used for cases such as this in which the diabetes is mild. Similar tuberous xanthomas have occurred in patients who had no diabetes, and frequently they have responded to restriction of the intake of fat. Nicholson's patient previously had not been on a diet unusually high in fat and although glycosuria existed there was no ketosis. It

7 Thiersch, H. Die Einwirkung des Knoblauchs auf die experimentelle Cholesterin-Atheromatose des Kaninchens. *Ztschr f d ges exper Med* 99: 473-477, 1936.

8 Nicholson, W. M. Xanthoma Diabeticorum. *Internat Clin* 4: 71-77 (Dec) 1937.

is true that improvement in the xanthomatous eruption followed control of the diabetes, but this control involved restriction of the intake of fat to 40 Gm, which perhaps was more responsible than anything else. Nicholson admitted that the relation in the case of the symptoms of the Cushing syndrome was speculative, and even though Anselmino and Hoffmann claimed, as he said, that extracts of the anterior lobe of the pituitary gland cause hypercholesteremia and ketonemia, their work is not fully substantiated. Hypercholesteremia and ketonemia are not characteristic of the Cushing syndrome, and in Nicholson's case there was no ketonemia. Values for cholesterol (total) of more than 300 mg per hundred cubic centimeters are rarely obtained for patients with uncomplicated diabetes except when they are in acidosis, and most instances of eruptive xanthomatosis that occur in diabetes are found in patients with acidosis with higher values than this. It seems to me that the term xanthoma diabeticorum might be reserved for them and that cases like that which Nicholson has reported represent an independent disease.

Campbell⁹ made the suggestion that a lasting increase in the content of blood fats in diabetes results not when more fat is obtained from the food but when there is an extreme demand for fat as fuel because of the absence of available carbohydrate. Much evidence supports this, however, even in diabetic acidosis values for total cholesterol of more than 300 mg do not occur with any regularity. In only 22 of Joslin's 94 cases of "coma" did the value exceed that figure.

Xanthomas of the skin are seen infrequently in diabetes, even when the values for the serum lipids are elevated. Nicholson mentioned 1 such instance, a patient at Duke Hospital had a markedly elevated fat content (total cholesterol, 990 mg, per hundred cubic centimeters, cholesterol esters, 513 mg, and total lipids, 8,136 mg). Marked lipemia apparently will not produce damage to reticular cells unless these originally are inadequate.

Normal Variations in Serum Lipid Values—Studies from the department of psychiatry of the Yale University School of Medicine by Man, Gildea and their associates¹⁰ indicate that the levels of the lipids of the serum are affected by malnutrition and by fat meals and that they usually are higher for healthy men of pyknic build than for those of the leptosomatic type, but that for the same subject they vary from time to time. In a recent paper report was made of examination at intervals, for periods of three months to four years, of 4 healthy

9 Campbell, J. N. H. Critical Review. Cholesterol in Health and Disease, *Quart J Med* **18** 393-422 (July) 1925.

10 Man, Evelyn B., and Gildea, E. F. Variations in Lipemia of Normal Subjects, *J Biol Chem* **119** 769-780 (July) 1937.

men and 6 healthy women. The extreme range for the cholesterol values of the serum was from 173 to 236 mg per hundred cubic centimeters, a difference of 31 per cent. The extreme range for lipid phosphorus values was 23 per cent and for fatty acids 37 per cent. That the differences were not related to hemoconcentration was shown by the fact that the values for the total protein of the blood were not affected in the same manner. No relation was found to the slight changes in weight which occurred in several of the subjects, to the season of the year or, in the case of the women, to the menstrual cycle. The fact is consistent with the usual wide range of normal cholesterol values described by Page, Kirk, Lewis, Thompson and Van Slyke¹¹. In cases of malnutrition, on the other hand, when the cholesterol values were found to be below normal for 26 of 31 patients, they varied widely with the state of nutrition in 10 patients who were followed for two to ten weeks, improvement in nutrition was accompanied with an increase of from 32 to 101 mg per hundred cubic centimeters, even when the first observations were not below the normal range. This and the progressive and consistent variations in the cholesterol values observed by Hurxthal¹² and others after the administration of thyroid to patients with myxedema, after the administration of iodine to patients with hyperthyroidism and after treatment of patients in diabetic acidosis are in sharp contrast to the unaccountable variations of lesser degree shown by the normal subject.

Serum Lipid Values in Diabetes—In a study of 79 diabetic patients who had no acidosis, Man and Peters¹³ found the values of the serum for cholesterol to be normal for 42, below normal for 9 and above normal for 28. There was close correlation with the values for phospholipids, and there was less correlation with the values for fatty acids, but gross changes in one component were reflected in the other. "*The value for cholesterol did not appear to be related to the severity of the diabetes, the fat in the diet or the degree of arteriosclerosis*". The subnormal values appeared for the most part associated with hypoproteinemia in patients who were malnourished. Moderate elevation was observed in obese women, but it appeared to be related to the pattern of obesity rather than to the diet.

Severe hypercholesteremia when encountered in these cases usually was referable to complications. It also occurred in a group of patients

11 Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and Van Slyke, D. D. Plasma Lipids of Normal Men at Different Ages, *J. Biol. Chem.* **111** 613-639 (Nov.) 1935.

12 Hurxthal, L. M., cited by Man and Gildea,¹⁰

13 Man, Evelyn B., and Peters, J. P. Lipoids of Serum in Diabetic Acidosis, *J. Clin. Investigation* **13** 237-261 (March) 1934.

with instability of the vasomotor reactions. Acromegaly existed in 1 case, but in the great majority it was impossible to implicate the pituitary body. In some cases there were symptoms suggesting a lesion of the brain stem (Parkinson syndrome, diabetes insipidus or some other condition). The basal metabolic rate frequently was elevated, nevertheless most of the stigmas of hyperthyroidism were lacking.¹⁴

Serum Lipid Values in Diabetic Acidosis—In diabetic acidosis, dehydration is responsible for many of the abnormalities encountered, including those in the values for the lipids of the blood. Changes in the values for lipids before and after treatment were compared by Man and Peters,¹⁵ with variations in the concentration of serum protein, which were taken as an index of the degree of dehydration. They had demonstrated before that normal capillaries are equally impermeable to proteins and lipids. In 15 cases of diabetes at the height of acidosis the values for cholesterol were above the normal levels for the subjects in question. They fell rapidly during recovery, their fall being paralleled by the course of the values for serum protein in all cases except 3, in these 3 cases the fall was greater than that of the value for protein. The reductions in the values for nonphospholipid fatty acids and lipid phosphorus exceeded those for cholesterol in most cases. The cholesterol value during the height of acidosis was greater than 300 mg per hundred cubic centimeters in only 5 cases, and when correction was made for hemoconcentration this was true in only 3 cases. Man and Peters, like Campbell, found reason for connecting the increases in the value for fatty acid with carbohydrate starvation, which by increasing the demand for consumption of fat provokes a mobilization of nutritive lipids from depots in the body. This theory they attributed to Blx,¹⁶ who before the introduction of insulin observed that the values for lipids in the serum of diabetic patients were higher before breakfast on the morning after a fast day than they were several hours after the ingestion of bread alone or a breakfast containing 35 to 50 Gm of fat.

Evidence for a direct effect of insulin on the fatty acids of serum has been sought by a number of investigators with results, according to

14 The question of the relation of cholesteremia to the arteriosclerosis of diabetes, with particular reference to the studies of Duff, Weiss and Minot, Watson and Wharton, and Hunt, who also concluded that the values for blood lipids are not related to the degree of arteriosclerosis in diabetes, was considered in a previous review (Wilder, R. M. Diseases of Metabolism and Nutrition, Arch Int Med 57 434-435 [Feb] 1936).

15 Man, Evelyn B., and Peters, J. P. Serum Lipoids in Diabetes, J Clin Investigation 14 579-594 (Sept) 1935.

16 Blx, Gunnar. Studies on Diabetic Lipemia, Acta med Scandinav 64 142-259, 1926. Page 234 is of particular interest.

Man and Peters, which are unconvincing. Man and Peters reported that for 10 of their patients who did not have acidosis no difference could be demonstrated between the values for the lipids of the serum before and those obtained one hour after the morning dose of insulin. Thus, what decrease in blood lipid value occurs after treatment of acidosis, beyond that which can be ascribed to hemodilution, is to be attributed, they claimed, to the recognized effect of insulin on carbohydrate metabolism, rather than to any supposititious direct effect on the mobilization or combustion of fat.

Serum Carotene—Frequently in conditions associated with hyperlipemia, whether xanthomatosis is present or not, the serum and the skin of the patient are yellowed by xanthochrome pigments (carotene and xanthophyll). In a study of the subject made several years ago in the division of medicine of the Mayo Clinic, Boeck and Yater¹⁷ found that in 100 patients with diabetes and 53 patients suffering from other diseases chosen at random, xanthemia occurred in 86 per cent of those with diabetes, in 100 per cent of those with renal disease and in 89 per cent of those with miscellaneous diseases. Xanthosis, on the other hand, defined as yellowing of the skin due to the deposit of lipochrome pigments, was present in 9 per cent of the patients with diabetes (2 of these patients also had xanthomatosis), in 9 per cent of those with renal disease and in 3 per cent of those with other diseases. Of 36 patients whose condition originally was diagnosed as xanthosis, 10 were diabetic and 26 either had other diseases or, with the exception of the xanthosis, were normal. Thus, these conditions are by no means to be considered manifestations of diabetes, as originally was supposed by von Noorden. Apparently there is a greater tendency for xanthosis to develop when the diabetes is severe, but even severe diabetes may not reveal this complication, and the evidence does not warrant the conclusion that the presence of xanthosis in diabetes unfavorably affects the course of the disease.

What causes xanthosis is unknown. It occurs more commonly when the diet has a high lipochrome content, but individual variation must exist in the ability to oxidize and excrete the pigments, because many patients show neither xanthemia nor xanthoses with diets equally high in lipochromes. There also is insufficient evidence at present to permit attributing the phenomenon to any fault in the metabolism of fat, although xanthosis usually accompanies hyperlipemia and xanthomatosis, it also occurs independently. The ease of oxidation of the pigments themselves is the probable explanation. Palmer¹⁸ showed that

17 Boeck, W. C., and Yater, W. M. Xanthemia and Xanthosis (Carotinemia). A Clinical Study, *J. Lab. & Clin. Med.* **14** 1129-1143 (Sept.) 1929.

18 Palmer, L. S. Carotinoids and Related Pigments. *The Chromolipoids*, New York, The Chemical Catalog Co., 1922.

oxidation accounts for the normal disappearance of these pigments in both human beings and animals

Heymann,¹⁹ after determining the content of carotene in the blood serum at intervals after the administration of carotene in oil to 10 diabetic and 12 nondiabetic children, concluded that carotene metabolism is interfered with in diabetes, and Ralli and her co-workers²⁰ have come to the same conclusion. They explained that the difficulty is due to failure of the liver to convert carotene to vitamin A but offered what seems to me insufficient evidence to establish such a conclusion.

Importance of Fat in Nutrition—It is important not to be overly alarmed by the evidences of injury from fat foods. It must be remembered, as the Buris and Miller²¹ have emphasized, that the diet of human beings often is exceedingly low in fats of any kind and that many fats in use today contain few acids more unsaturated than oleic acid. It is not improbable that diets high in carbohydrate and protein, by carrying an inadequate amount of unsaturated oils, are contributory factors to the development of dry skin, disturbed renal function, sterility, anemia and other pathologic conditions. The liver apparently is limited in its ability to produce unsaturated fatty acids, and the latter must be obtained through the diet.

OBESITY

Digestion and Absorption of Fat in Obesity—This subject requires periodic attention because of the popular misconception that obese persons derive more value from the food they eat than do thin persons. Neuenschwander-Lemmer²² determined the caloric values of the feces and their content of nitrogen and of fat for 3 obese and for 3 control subjects who were of normal weight. The intake of calories purposely was held somewhat below the calculated requirements, and rest in bed was maintained. Under these circumstances the percentage of utiliza-

19 Heymann, Walter. Carotenemia in Diabetes, *J A M A* **106** 2050-2052 (June 13) 1936

20 Ralli, Elaine P., Brancialeone, H., and Mandelbaum, T. Studies on Effect of Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus. Effect of Oral Administration of Carotene on Blood Carotene and Cholesterol of Diabetic and Normal Individuals, *J Lab & Clin Med* **20** 1266-1275 (Sept.) 1935. Stueck, G. H., Flaum, Gerald, and Ralli, Elaine P. The Serum Carotene in Diabetic Patients, with Clinical Evidence of Carotenemia as Determined by the Photo-Electric Colorimeter, *J A M A* **109** 343-344 (July 31) 1937.

21 Burr, G. O., Burr, Mildred M., and Miller, E. S. On the Fatty Acids Essential in Nutrition, *J Biol Chem* **97** 1-9 (July) 1932.

22 Neuenschwander-Lemmer, N. Ueber Ausnutzungsversuche bei fettsuchtigen und normalen Menschen, *Ztschr f d ges exper Med* **99** 394-398, 1936.

tion by the obese persons averaged 87 for calories, 84 for nitrogen and 83 for fat. The corresponding figures for the controls were 88, 85.5 and 85.5 per cent, respectively. The figures for absorption for both groups were somewhat below those obtained by Atwater. For normal men they were 88.3 to 97.4 per cent for calories, 88.3 to 96.2 per cent for nitrogen and 87.3 to 98.3 per cent for fat.

Ketomuria and Obesity—Lauter and Neuenschwander-Lemmer,²³ unable to confirm an observation of Kugelman supporting Bergmann's theory of *lipomatoesen Tendenz*, have reported that fat persons respond to feeding with fat oil with a higher than normal concentration of acetone bodies in the blood. On the other hand, support for the conception that in some cases of obesity the stored fat is less available for oxidation has been presented by MacKay and Sherrill,²⁴ who studied the ketonuria exhibited during fasting by 11 obese and 5 normal subjects. The fasts lasted for four or five days. Four of the obese subjects, whose condition was classified for other reasons as endocrinopathic, excreted appreciably less ketone in grams per square meter of body surface than did normal subjects. For the remainder, whose overweight was classified as simple obesity, the excretion always was great and was usually greater than that for the normal subjects. The authors proposed that the method probably offers a means of classifying obesity on a physiologic basis. "Locked fat," they concluded, is a result of endocrine disturbance, this being suggested by the observation of MacKay and Barnes²⁵ of the ketogenic activity of certain anterior pituitary extracts and by the demonstration by Best and Campbell²⁶ that such extracts promote the transportation of fat from the body stores to the liver.

These reports still remain difficult to harmonize with clinical observations. For instance, 2 obese women with a low value for ketone bodies in the urine, reported on by MacKay and Sherrill, "gathered their fat quickly following evidence of ovarian deficiency." If this deficiency represented a phenomenon of the menopause, the anterior lobe of the pituitary gland should have been overactive rather than underactive, and thinness rather than obesity should have been expected. As a matter of fact, whether a woman will become thinner or fatter with the development of ovarian deficiency is unpredictable.

23 Lauter, S., and Neuenschwander-Lemmer, N. Ueber den Ketonkörpergehalt des Blutes bei Fettsuchtigen und Normalen. *Ztschr. f. d. ges. exper. Med.* **99** 745-748, 1936.

24 MacKay, E. M., and Sherrill, J. W. A Comparison of the Ketosis Developed During Fasting by Obese Patients and Normal Subjects, *Endocrinology* **21** 677-680 (Sept.) 1937.

25 MacKay, E. M., and Barnes, R. H., cited by MacKay and Sherrill.²⁴

26 Best, C. H., and Campbell, J., cited by MacKay and Sherrill.²⁴

Another Theory of Obesity—Even though one grants, as one must, that the caloric balance will determine in the end whether fat is deposited or released from storage in the body as a whole, there still remains to be explained why in some cases fat accumulates selectively in certain regions of the body. It is well known that the fat in lipomas is resistant to withdrawal for utilization even in starvation, also that starvation in cases of lipodystrophy causes a much greater loss of fat from the thin upper half of the body than from the fat legs and buttocks. Hetenyi²⁷ recently advanced the following evidence in support of Bergmann's theory, according to which the tissues of obese persons possess an increased "lipophilia"

Eighteen patients, 10 of them normal in weight and the others obese, were placed for eight days on a subnutrition diet consisting of 800 Gm of milk and ten crackers. The lipid level of the blood of the subjects of normal weight was unchanged in general, whereas that of the obese subjects fell 18 to 43 per cent. Also, 30 subjects, 13 of them obese and the others normal in weight, were given in the morning, without other food, 200 Gm of cream, representing approximately 60 Gm of fat. For the obese subjects the lipid level of the blood, determined after two, three, four and five hours, increased significantly less than did that for the subjects of normal weight. Also, artificial fever was produced in 12 subjects, 5 of them normal and 7 obese. The content of fat in the blood was increased thereby 15 to 36 per cent for the normal subjects and up to 11 per cent for the obese subjects. Finally, 50 cc of olive oil was injected subcutaneously into each of 11 subjects, 6 of them obese, and the level of blood lipid was determined at the second, fourth and sixth hours. It increased at one time or another 10 to 48 per cent for the normal subjects and only 1 to 8 per cent for the obese. Among the patients who were given injections of oil were 2 with lipodystrophy. When the oil was injected into an upper extremity in these cases absorption proceeded as in the normal subjects, when it was given into a fatty lower extremity the absorption was similar to that in the obese subjects.

These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. The condition seems analogous to the increased stability of deposits of glycogen in the liver and in the muscle in von Gierke's disease (glycogenosis). It seems to me that this conception deserves attentive consideration. The effect after meals of withdrawing from the circulation even a little more fat than usual might well account both for the delayed sense of satiety and for the frequently abnormal taste for

²⁷ Hetenyi, G. Untersuchungen über die Entstehung der Fettsucht, *Deutsches Arch. f. klin. Med.* **179** 134-141, 1936.

carbohydrate encountered in obese persons. Energy requirements must be satisfied one way or another, and if part of the food is made less available for metabolism, the result, as is the case in diabetes, inevitably is hunger. A slight tendency in this direction would have a profound effect in the course of time. The theory also will explain the unequal distribution of fat and the undoubted influence on this distribution of the endocrinopathies, thus harmonizing the point of view of those who have insisted on the primacy of the dynamic features of the problem with the point of view of those who stress its endocrinologic and constitutional features.

Hereditv in Obesity—There is a strong disinclination on the part of physicians to accept the thesis, defended most effectively by Newburgh and his associates,²⁸ that obesity always depends on overeating. So-called endogenous obesity is still regarded by many persons as an entity in which the law of conservation of energy fails to function. What seems mostly to be neglected by those who hold such views is the fact that the water balance in obesity which is associated with endocrine disturbances of various kinds frequently is very unstable. However, heredity must play a part of some kind, and the thing that is inherited, as I²⁹ have suggested previously, is abnormal irritability in centers of the diencephalon where feelings of hunger and satiety originate. A lesion in this region, such as is produced by encephalitis or a tumor, is followed not uncommonly by a huge gain in weight. Experimental lesions of the diencephalon also have been shown to provoke obesity, so that it seems likely that the degree of irritability of this region may differ within a physiologic range in different normal persons and that the characteristic may be passed from parent to child, much as unusual auditory sensitiveness is known to be transmitted. Supporting this supposition is a report by Gurney³⁰ of studies on 63 stout women compared with another group of women of approximately the same age periods who had been subjected to about the same physiologic and physical episodes. Pregnancy or a major operative procedure appeared to be the most common factor associated with the onset of obesity in the group of stout women, but approximately the same incidence of these events did not have a like effect in the control group. On the other hand, the incidence of obesity in the parents of the stout women was markedly greater than that in the parents of the controls,

28 Newburgh, L. H., and Johnston, M. W. Endogenous Obesity. Misconception, *Ann Int Med* **3** 815-825 (Feb.) 1930, Nature of Obesity, *J Clin Investigation* **8** 197-213 (Feb.) 1930.

29 Wilder, R. M. Regulation of Weight of the Body, *Internat Clin* **1** 30-41 (March) 1932.

30 Gurney, R. The Hereditary Factor in Obesity, *Arch Int Med* **57** 557-561 (March) 1936.

and a study of the progeny of the two groups showed the following differences. Seventy-three per cent of the 89 offspring from matings of stout persons were stout whereas only 9 per cent of the 176 offspring of the matings of nonstout persons were stout. Forty-one per cent of the 107 offspring of a stout and a nonstout person were stout.

Joslin has said that he is inclined to attribute the frequency of stoutness in the children of obese parents to habits acquired from eating with the parents rather than to heredity, certainly stout persons appreciate good food more than do nonstout persons, and their children thus are "exposed" to better food. What epicure would hire a thin cook! However, it is probable that something more than habit is involved and that this something, which is acquired by inheritance, gives the stout man a better as well as a more discriminating appetite.

Appetite and Control of Body Weight—My interest in this subject was aroused again by a paper of MacLagan³¹ in which are described experiments with rabbits fed a standard ration of beef pulp, bran and water. The appetite of these animals, for the purpose of description, was defined according to the amount of food eaten in a standard time when an unlimited supply was presented. It normally reached a maximum when the animals had fasted eighteen hours, being less if the fast was longer or shorter than this period. An increase of about 20 per cent was produced by a period of ten days of undernutrition, and an increase of 10 per cent was produced by giving insulin in doses of 10 units. This dose is nearly convulsive in a fed rabbit, and smaller doses were without effect. Maximal depression of the appetite, amounting to 49 per cent, was obtained by giving pitressin in doses of 5 units. Almost as effective depression occurred with a dose of 0.15 Gm. of atropine, namely, 37 per cent. Ephedrine, in a dose of 0.15 Gm., was only slightly depressing, and enterogastrone, an extract of intestinal mucosa, had a temporary effect. Negative results were obtained with pitocin, anterior pituitary extract, "ketodestrin," testicular extract and benzedrine. The conclusion is reached that the effect of these drugs on the appetite is likely to be of no clinical value, except for that of insulin, which already has been widely used for treating thinness. Pitressin and atropine had to be given in rather large doses to produce any effect, the former causing slight diarrhea in 3 of 8 animals and the latter causing full dilatation of the pupils in the doses employed.

Dinitrophenol—This remedy for obesity apparently has run its course, and the consensus seems to be that the danger attending its use outweighs the advantages. The comprehensive clinical study reported

³¹ MacLagan, N. F. The Role of Appetite in the Control of Body Weight, *J. Physiol.* **90** 385-394 (Sept.) 1937.

by Simkins³² should be read by any one who contemplates resorting to this drug. The final comment of Simkins was as follows:

In dinitrophenol the medical profession has acquired a remarkable drug, a metabolic agent that is well adapted to both clinical and laboratory research. The problems connected with its unpredictable, and occasionally alarming, reactions in some patients are far from solved. Apparently it is nontoxic to the liver, kidneys and heart in therapeutic dosage. Neutropenias are rare. Peripheral neuritis is rather common but not troublesome. Skin rashes, which are common, no longer excite their quondam fear. Cataracts, whether due to the direct effects of the drug or possibly to some unknown mechanism mediated by it, are common. No loss of weight can be condoned at the price of cataracts, and consequently the indiscriminate clinical use of dinitrophenol should be discontinued at once until the problem of complicating cataracts is solved. The clinical use of dinitrophenol should be reserved for urgent indications only.

Exercise for the Obese Person—Douthwaite,³³ in one of a series of articles on the management of patients with some of the metabolic diseases, has given the following excellent advice:

Most exercises advised for fat people are almost useless, and in many cases very wasteful of physical effort for the result achieved. Thus, the contortions made familiar to us from our young days by the gymnasium instructor often produce powerful biceps, a deep chest, and strong abdominal recti. They leave out of account entirely the importance of the oblique muscles of the abdomen and the quadratus lumborum. It is the weakening of these muscles, however, which is responsible for the loss of waist line, pendulous belly, and constipation of those possessed of a redundant paunch. Another objection to current bathroom exercises is that they can be practised only in strict privacy, for their employment in the street would inevitably lead to an observation cell.

What, then, are the exercises which we should advise? In the first place, they must involve all the main muscles of the abdominal wall and pelvic floor. Secondly, it should be possible to carry out some of them, at any rate, *during working hours* without attracting undue attention. In my opinion those described by Hornibrook in "The Culture of the Abdomen" are far and away the best. This book is a better prescription for abdominal obesity, and for that matter for constipation, than any drug or combination of drugs. The principle is this: the abdominal muscles can be contracted and relaxed at will without causing gross movements of the trunk. The viscera, however, are thus kept in healthy turbulence, and fat deposits over and in these muscles steadily disappear. The action is much the same as that which produces contraction of the quadriceps femoris without accompanying extension of the knee-joints.

First, the patient should be taught to pull his abdominal wall in and out while standing and while sitting. This activates the recti chiefly, but also to some extent the obliques. Secondly, he should learn to exercise the obliques and quadratus lumborum by standing and drawing the hips and lower ribs together, first on one side then on the other. This is more difficult to learn and at first involves more

32 Simkins, Samuel. Dinitrophenol and Desiccated Thyroid in the Treatment of Obesity. A Comprehensive Clinical and Laboratory Study, J A M A 108 2110-2117 (June 19), 2193-2199 (June 26) 1937.

33 Douthwaite, A. H. The Treatment of Obesity, Brit M J 2 344-346 (Aug 15) 1936.

movement, but in time the action can be mastered so that the lateral and posterior abdominal muscles are alternately contracted and relaxed with but little motion of the trunk. Again, they can be carried out eventually in a sitting posture. The patient should be taught to appreciate what is happening by placing his fingertips over the muscles to be exercised. By this means he will grasp the scheme much more quickly and carry it out more efficiently. Thirdly, the pelvic floor should be exercised by alternately drawing up and relaxing the anus. As a sharp contraction of the relevant muscles takes place in both sexes at the end of defaecation and of micturition it can be explained in this way without difficulty. The reason for these exercises is that the pelvic floor is usually weakened in the obese and tends to the production of incontinence of urine in the female, constipation, rectal prolapse and piles.

Lastly, the back must not be forgotten. All fat people eventually develop a bad stance, and a healthy abdominal wall cannot be achieved if its main point of attachment is weak and warped. Insistence should thus be placed on the importance of carrying the head and body erect as a positive means to the desired goal. Now, although many other excellent exercises have been devised, yet only those described above can easily be carried out from time to time during the day. The muscular contractions can be performed while the patient is traveling, while waiting for a bus, sitting at a desk, and even at the dinner table, without exciting comment. The great secret of successful exercises is that they should be capable of being performed at frequent intervals until they become a habit. This is obviously of far greater value than a quarter of an hour's intense boredom of "bedroom jerks."

EXPERIMENTAL DIABETES

Metabolism of Carbohydrate in Depancreatized Dogs—It is doubtful how much dependence can be placed on metabolic observations made after a severely mutilating operation such as that to be described. Soskin and Levine³⁴ reported experiments performed on dogs that had fasted for three days and that were then subjected to surgical removal of the intestines and the liver, together with ligation of the ureters. Twelve dogs were depancreatized on the first day of fasting, receiving no insulin. Fifteen dogs were not depancreatized. The evisceration and later experiments were performed with the animals under anesthesia induced by pentobarbital sodium. After two hours had been allowed for recovery from immediate shock, the experiments were started. Dextrose solution was injected at the timed rates necessary to maintain blood sugar at desired levels and samples of blood were taken at half-hour intervals for two to four hours. After the injection the animals were killed, and samples of muscle were secured for determination of the glycogen content. The results showed that when the blood sugar level was high, the depancreatized animals used dextrose as effectively as did the "normal" animals, when the blood sugar level was low, the depancreatized dogs were at a disadvantage. This led

34 Soskin, S., and Levine, R. A Relationship Between the Blood Sugar Level and the Rate of Sugar Utilization Affecting the Theories of Diabetes, *Am J Physiol* **120** 761-770 (Dec) 1937

Soskin and Levine to the conclusion that the completely depancreatized dog utilizes dextrose as effectively as the "normal" animal and hence supports their assumption that the glycosuria and the other characteristic experimental and clinical phenomena associated with diabetes cannot be ascribed to lack of utilization of sugar by the muscles

Mirsky and his associates³⁵ have reported that dextrose injected intravenously into nephrectomized depancreatized dogs not receiving insulin produces ketolytic and nitrogen-sparing effects. The conditions of the experiment were such as to lead to the suggestion that glycogen formation occurred. A similar study has been conducted by Barker and Sweet³⁶ in such a manner that the respiratory metabolism could be studied as well as the blood. It was found that while pronounced ketone and nitrogen sparing was obtained, the respiratory quotient was not raised and that all the sugar injected could be accounted for by the increased amount of fermentable carbohydrate and lactic acid in the muscle and liver. Some explanation other than oxidation of carbohydrate may be found for the nitrogen-sparing and ketolytic effects observed under the conditions named. As the authors commented

It should first be pointed out that decreased protein metabolism is judged in this type of experiment solely on the basis of changes in blood non-protein nitrogen, any unmeasured retention of urea in the liver or in the muscles would give a false picture. Secondly, since protein is ketogenic in pancreatic diabetes, any lowering of protein breakdown might account for some of the ketone sparing. In any case, these changes may be attributed fully as well to the high glucose concentrations produced as to the glycogen deposited.

The experiments indicate that neither the formation of glycogen nor the establishment of a high carbohydrate level of the tissues facilitates the oxidation of sugar by the depancreatized dog.

The commonly accepted criteria for oxidation of ingested carbohydrate are an elevation in respiratory quotient, a corresponding diminution in the amount of extra sugar excreted when dextrose is administered, a protein-sparing action of the sugar and a ketolytic effect. Recent experiments of Barker, Chambers and Dann,³⁷ conducted on fasting depancreatized dogs, revealed that in the early and intermediate stages there occurred no rise in the respiratory quotient, no nitrogen-sparing effect and no ketolytic action after the administration by mouth of 16

35 Mirsky, I. A., Heiman, J. D., and Broh-Kahn, R. H. The Antiketogenic Action of Glucose in the Absence of Insulin, *Am J Physiol* **118** 290-296 (Feb.) 1937. Mirsky, I. A., Heiman, J. D., and Swadish, S. The Nitrogen-Sparing Action of Glucose in Phlorhizin and Pancreatic Diabetes, *ibid* **119** 376-377 (June) 1937.

36 Barker, S. B., and Sweet, J. E. Effects of Carbohydrate Plethora in Experimental Diabetes, *Science* **86** 270-277 (Sept. 17) 1937.

37 Barker, S. B., Chambers, W. H., and Dann, Margaret. Metabolism of Carbohydrate in the Depancreatized Dog. *J Biol Chem* **118** 177-195 (March) 1937.

to 50 Gm of dextrose in single or divided doses. Also, the extra dextrose recovered in the urine averaged 95 per cent for twenty-one experiments. These results indicated no oxidation of administered sugar. However, in 3 animals in the last stages of inanition, indicated by markedly increased excretion of creatine, typical effects of carbohydrate oxidation were obtained. In 1 of these animals the fasting level for blood sugar was 37 mg per hundred cubic centimeters and the basal respiratory quotient 81 per cent. In this animal, only three days before the premonitory condition, the dextrose test had shown complete lack of oxidation of carbohydrate.

This work, as Barker and his associates indicated, recalls experiments of Hedon³⁸ in which bread was fed to depancreatized dogs and the fact that high basal quotients were observed by him in the "premonitory" stages of fasting. The terminal phases of diabetes in patients who were treated with prolonged fasts in the era before insulin was discovered and who showed hypoglycemia and an elevated respiratory quotient represented the same phenomenon. A famous case in point was that of Cyril K., who was studied intensively at the Russell Sage Institute of Pathology.

Barker and his associates also referred to the fact that Houssay and Biasotti³⁹ in 3 of 5 depancreatized dogs found the respiratory quotient to be elevated from a basal level of 0.7 to approximately 0.8 after a feeding of 50 Gm of dextrose. Similar results were obtained by Biasotti for 2 more such animals after intravenous injection of sugar.

A plausible explanation of the paradoxical ability of the moribund organism to oxidize dextrose is provided by these and other recent experimental observations. Extreme cachexia, it is reasonable to suppose, must severely depress not only the activity of the pituitary gland but also the activities of the adrenal cortex and of the thyroid gland. The latter may be involved directly or secondarily as a result of depression of activity of the pituitary gland. It is well known that both the thyroid gland and the adrenal bodies undergo a considerable degree of atrophy when the pituitary gland is destroyed. Under these circumstances the antagonists to what limited primordial capacity the cells may natively possess for oxidizing dextrose are removed, and, in addition, presumably by the same means, the activity of the liver in neodextrogenesis is depressed.

PROTAMINE ZINC INSULIN

Retarded insulin continues to receive much attention in the current journals. I can attempt to review only a few of the many papers now dealing with the subject. The opinion prevails that treatment is improved

38 Hedon, cited by Barker, Chambers and Dann³⁷

39 Houssay, B. A., and Biasotti, A., cited by Barker, Chambers and Dann³⁷

by its use, although occasional patients respond less favorably than others. A comment of Whitehill and Harrop⁴⁰ was that patients who are not cooperative and who are lax in the management of their diet do badly with protamine zinc insulin and that such patients will find the use of unmodified insulin safer and on the whole more satisfactory. Also in cases in which diarrhea is a complication and in which absorption of food from the bowel is variable, they said they regard protamine zinc insulin as unsafe. Sherrill and Cope,⁴¹ while admitting that it represents a distinct advance in diabetic treatment, questioned whether any particular advantage is to be gained from it in cases in which formerly an essentially normal balance could be maintained with unmodified insulin. The consensus seems to be that treatment, while improved, has not been simplified. Warvel and Shafer⁴² emphasized that the use of protamine zinc insulin requires more effort on the part of the physician.

In cases of more severe diabetes it rarely is possible to obtain satisfactory control with one dose of protamine zinc insulin alone. It thus frequently is necessary also to use some unmodified insulin with it. From experience at the Mayo Clinic and that of Joslin⁴³ it has been found that the two cannot effectively be combined in the same syringe, and although Lawrence and Archer⁴⁴ reported that they had combined them with advantage, I advise against it. Patients find it difficult enough to learn how to measure insulin accurately, and to teach them to draw into one syringe the required amount of one insulin and then to supplement this with a proper amount of a second insulin in most cases is impossible.

Protamine zinc insulin of 80 unit strength recently has been distributed for clinical trial. According to Joslin, and experience at the Mayo Clinic has been the same, it acts just as efficiently as the preparation of 40 units strength heretofore available. Joslin also said that it is less likely to cause induration in the skin. Somewhat more care is necessary to secure a uniform suspension before the dose is withdrawn from the vial, it has a slightly greater tendency to form small clumps.

40 Whitehill, M. R. and Harrop, G. A. Experience with Protamine Zinc Insulin. *South M. J.* **30** 451-458 (May) 1937.

41 Sherrill, J. W., and Cope, E. F. F. Observations with Protamine Zinc Insulin and Experimental Studies, Publication of the Scripps Metabolic Clinic, La Jolla, California.

42 Warvel, J. H. and Shafer, M. R. Protamine Insulin in the Treatment of Diabetes Mellitus, *J. Indiana M. A.* **30** 325-332 (July) 1937.

43 Joslin, E. P. Protamine Insulin. *J. A. M. A.* **109** 497-503 (Aug. 14) 1937.

44 Lawrence, R. D., and Archer, N. Zinc Protamine Insulin. A Clinical Trial of the New Preparation. *Brit. M. J.* **1** 487-491 (March 6) 1937.

Magnitude of Doses—Actually in the experience at the Mayo Clinic there has been less use for 80 unit strength protamine zinc insulin than was anticipated. The diets used as a routine contain only about 150 Gm of carbohydrate, and with this regimen the large majority of patients require less than 50 units daily. Those that do take more for the most part are unstable, with unpredictable fluctuations in their requirements, for them a safer procedure seems to be to use not more than 50 units of protamine zinc insulin and to depend on one or more injections of supplementary unmodified insulin for the additional requirement. However, other physicians with experience are resorting to much larger doses of protamine zinc insulin. Thus, Duncan⁴⁵ said that single doses of 80 to 120 units are not uncommon, and in 1 of several cases of juvenile diabetes reported by Drysdale⁴⁶ a balance was obtained with 140 units daily.

Timing the Administration—The administration of protamine zinc insulin in one dose daily before breakfast, as originally advocated by American and Canadian physicians,⁴⁷ has been widely adopted. The principal advantage therein is that a single specimen of urine, that passed before breakfast, then provides a reliable guide to dosage. If it contains sugar, the dose may be stepped up with safety, if it is free from sugar the possibility of overdosage must be considered, and after a few days with sugar-free morning urine the patient should be given a smaller dose. Treatment with protamine zinc insulin, as Himsworth⁴⁸ stated, should have as its first objective the control of the disease during the night and only as a secondary objective the restraint of the exaggerated rises in the sugar content of the body after meals. Lawrence and Archer have expressed the same opinion. Referring to the possibility of securing better results with insulin of still longer action, they suggested that this drug would produce a condition comparable to the late syndrome of spontaneous hypoglycemia and would provoke a reaction every night. "It is clear," they said, "that the basal dose must be tailing off in strength of action at night."

45 Duncan, G. G. Protamine Zinc Insulin and Its Practical Application in the Treatment of Diabetes Mellitus, *Bull. Ayer Clin. Lab. Pennsylvania Hosp.* **3**: 121-137 (June) 1937.

46 Drysdale, H. R. Protamine Insulin in Juvenile Diabetes, *J. A. M. A.* **108**: 1250-1257 (April 10) 1937.

47 Wilder, R. M. Clinical Investigations with Insulin Protamine Compound, *Proc. Staff Meet., Mayo Clin.* **11**: 257-258 (April 22) 1936. Campbell, W. R., Fletcher, A. A., and Kerr, R. B. Protamine Insulin in the Treatment of Diabetes Mellitus, *Tr. A. Am. Physicians* **51**: 161-173 (May 5) 1936.

48 Himsworth, H. P. Protamine Insulin and Zinc Protamine Insulin in the Treatment of Diabetes Mellitus, *Brit. M. J.* **1**: 541-546 (March 13) 1937.

On the other hand, Himsworth⁴⁹ is said recently to have obtained excellent results by administering protamine zinc insulin at 11 p. m., the food is then better utilized the next day, and Winnett,⁵⁰ for the same reason, has given injections two or three hours before breakfast.

Supplementary Doses of Unmodified Insulin—Waivel and Shaffer found that the single morning injection of protamine zinc insulin was satisfactory for adults taking not more than 30 to 35 units but that supplementary doses of unmodified insulin were required before breakfast and before supper by patients with more severe diabetes. Himsworth agreed. He wrote:

It is only in mild cases that the new preparations may legitimately be expected to control the disease during the whole twenty-four hours. In cases of severity their action should be reinforced by the administration of ordinary insulin at those times when a sudden influx of sugar from the intestine is found to overwhelm their mild action. An analogy may be drawn between the use of the new insulin and a modern technic in anesthesia. The protamine insulins are comparable to the basal anesthetics whose effect is both mild and prolonged, ordinary insulin is comparable to the volatile anesthetic which is superimposed at times when a stronger control is required.

If one insists on having continuously sugar-free urine when only protamine zinc insulin is being used, chronic hypoglycemia is unavoidable, at least in many cases. The symptoms attending gradual lowering of the blood sugar level may be minimal, so that such hypoglycemia is not always easy to recognize. Conceivably, chronic hypoglycemia also may cause serious damage to the nervous system. I⁵¹ referred in last year's review to Bollman's observations of petechial hemorrhages in dogs that had been made hypoglycemic with protamine zinc insulin. His observation has been confirmed by Sherrill and MacKay.⁵² Six dogs which were kept in stuporous condition, with blood sugar values between 20 and 30 mg. per hundred cubic centimeters for twenty-four or forty-eight hours, died even after the value was raised to normal by the giving of sugar. A comment that is of interest and importance has been made by Greenhouse.⁵³ "Certainly some of our patients feel better when they show some sugar in the urine and feel quite uneasy when

49 Himsworth, H. P., cited by Joslin⁴⁷

50 Winnett, E. B. The Clinical Management of Diabetes Mellitus Using Protamine Zinc Insulin, *J. Iowa M. Soc.* **27** 150-154 (April) 1937.

51 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **59** 329-364 (Feb.) 1937.

52 Sherrill, J. W., and MacKay, E. M. Deleterious Effects of Insulin Shock, *Proc. Soc. Exper. Biol. & Med.* **36** 515-516 (May) 1937.

53 Greenhouse, B. Protamine Zinc Insulin, *Connecticut M. Soc.* **1** 247-252 (May) 1937.

sugar free" If by "some sugar" is meant not more than traces in the tests made later in the day and an occasional trace in the urine before breakfast, I wholeheartedly agree It seems to me to be important to discriminate between the glycosuria that follows a meal and that which occurs in the night The former represents the spill from an over-filled vessel, the latter is derived from the stores of glycogen and catabolizing protein Protamine zinc insulin, as I⁵⁴ have shown, prevents the occurrence of periods in the twenty-four hours, especially at night, when the tissues of the diabetic patient treated with insufficiently frequent doses of unmodified insulin are called on to deliver amino-acids for the manufacture of dextrose Ketosis accompanies the resulting negative nitrogen balance, and it too is avoided Lawrence and Archer have made a similar comment about protamine insulin

A striking feature is complete absence of ketosis throughout the twenty-four hours, much more complete than we have ever obtained by three doses of soluble insulin in severe cases of diabetes Even during the period of hyperglycaemia and glycosuria after a meal there is no recurrence of ketonuria as judged by the sensitive nitroprusside test It appears that the worst defect of diabetes, the endogenous production of new sugar and acetone bodies, is incomparably better controlled than ever before

In view of the nitrogen sparing attributable to the continuous insulin effect that is obtained with protamine zinc insulin and the conceivable danger from chronic hypoglycemia attending overdosage with it also because, like others, I have seen many patients who were "quite uneasy" when the urine was continuously free from sugar, it seems to me to be unwise when using protamine insulin to insist on a continuously normal value for blood sugar The procedure for adjusting the doses of insulin which I⁵⁵ recommend has been described elsewhere It probably will be disapproved of by Sindoni,⁵⁶ who has said he regards any degree of hyperglycemia as evidence of inability to oxidize dextrose—a debatable question Because protamine zinc insulin cannot be depended on to prevent the development of high blood sugar levels after meals, Sindoni has not prescribed it alone but only as an adjunct to unmodified insulin When it is indicated at all it should be given he has said, on retiring and if necessary also after breakfast, and, whether or not it is used, a dose of unmodified insulin is to be administered fifteen minutes after each meal Complete control of hyperglycemia he has maintained, will delay premature arteriosclerosis, will

54 Wilder, R M Clinical Investigations of Insulins with Prolonged Activity, *Ann Int Med* **11** 13-30 (July) 1937

55 Wilder, R M A Primer for Diabetic Patients, ed 6, Philadelphia, W B Saunders Company, 1937

56 Sindoni, A, Jr Protamine Insulin Versus Ordinary Insulin, *J A M A* **108** 1320-1327 (April 17) 1937

help to prolong the span of life and will increase resistance to infection. This may be true, but surely such radical control is impossible for the patient who lives at a distance, and if it is attempted away from the hospital it must involve great risk of insulin reactions or chronic hypoglycemia.

Another advocate of perfectly normal levels for blood sugar is Richardson,⁵⁷ who has suggested that if a renal threshold is higher than 180 mg per hundred cubic centimeters, examination of urine should not be depended on to direct the maintenance of a satisfactory adjustment. This, too, may be theoretically advantageous when the patient comes regularly to a clinic, it cannot apply to the isolated rancher, for instance, whose nearest laboratory may be several hundred miles away.

The Diet with Protamine Zinc Insulin — It has been the experience at the Mayo Clinic that better control usually is obtainable with protamine zinc insulin if not more than 150 Gm of carbohydrate is included in the diet. Campbell's experience and that of Joslin, referred to in last year's review,⁵¹ as well as that of Ricketts,⁵⁸ have agreed with it. However, Rabinowitch,⁵⁹ Duncan⁴⁵ and others have reported satisfactory results with diets containing as much as 300 Gm of carbohydrate. It is advantageous under such circumstances, and at times desirable even when less carbohydrate is given, to spread the meals, as Duncan has proposed, by giving the breakfast early, saving a portion of it to be taken in the forenoon and taking a lunch at midday, an afternoon snack, a late supper and food at bedtime. Joslin also has recommended more frequent supplying of food in meals and lunches. Greenhouse⁵³ has stated that he subtracts from the day's dietary prescription the value of three glasses of milk, one of which is given at 10 a. m., one at 3 p. m. and one at bedtime. Ricketts has subtracted a small amount of carbohydrate from the breakfast for a midmorning feeding, and in two thirds of his cases finds a bedtime meal to be a necessity. Pollack⁶⁰ has said that he gives no fruit other than banana at breakfast and some other fruit later in the morning. He has found the carbohydrate of banana to be absorbed more slowly than that of other fruits. Also, he has said that he gives two thirds of the protein of the dietary prescription at the evening meal and extra protein-containing food, such as cheese or meat, at bedtime.

57 Richardson, R., and Bowie, M. A. Observations on the Effectiveness of Protamine Insulin, *Am J M Sc* **192** 764-772 (Dec.) 1936. Richardson, R. Observations on Protamine Zinc Insulin, *ibid* **193** 606-611 (May) 1937.

58 Ricketts, H. T. Problems Connected with the Use of Protamine Zinc Insulin, *Ann Int Med* **11** 777-790 (Nov.) 1937.

59 Rabinowitch, cited by Wilder and Wilbur.⁵¹

60 Pollack, Herbert. Personal communication to the author.

These procedures undoubtedly are useful in "ticky" cases. I object to them for routine management because of the inconvenience they cause the patient. So far as possible one should strive to interfere as little as necessary with customary habits of eating and we in this country are not Europeans.

Protamine Zinc Insulin in Emergencies—A good many writers hold to the opinion that protamine zinc insulin is disadvantageous in the diabetic emergencies, such as acidosis, infection and operation. Exceptions to this view, as Ricketts has written, are emergencies which arise when patients are already under treatment with protamine zinc insulin. In such cases the basal dose should be continued, and the extra requirement should be met with multiple injections of unmodified insulin. At the Mayo Clinic⁵⁴ not only is protamine zinc insulin used in such circumstances, but a moderate dose of it is given in the initial treatment of acidosis and before an operation, even when none has been used before.

Complications Attributable to Protamine Zinc Insulin—Duncan has cited a personal communication from Dr. F. P. Peck, of Indianapolis, in which he stated that 6 cases of allergy to the protamine component of the new insulin have come to attention. I have not encountered it, although it is my impression that irritation at the site of injection occurs somewhat more frequently with protamine zinc insulin. Usually it does not occur after a few weeks of treatment. When necessary, "special" protamine zinc insulin made from beef can be obtained on application to the manufacturers of insulin. No instance of atrophy of fat has come to my attention, and it is to be hoped that this unsightly deformity will be of less frequent occurrence, owing to the fact that insulin is released from its combination with protamine only after absorption. Vascular accidents from the use of protamine zinc insulin also have not been reported, as far as I can determine.

OTHER INSULINS WITH PROLONGED ACTION

An interesting development was in progress in California at the same time that Hagedorn was experimenting with the protamines. For a number of years, in the division for research on cancer at the Santa Barbara Cottage Hospital, investigation of the relation of hormones to cancer has been carried out under the direction of Ullmann. In the course of this study Bischoff and Maxwell found a certain sample of pituitary gonadotropic extract to be fully ten times more potent than other samples. Eventually this was accounted for by traces of zinc left in the preparation during the process of separation. Eventually it was shown also that absorption of the hormone was retarded by the zinc and that the greater activity depended on this retardation. This

phase of the work was published by Maxwell⁶¹ The suggestion arose that the same principle might be applied with advantage to insulin, but first, because of apprehension on the score of possible toxicity from such a heavy metal, a search was made for other substances which would have the same effect as zinc Most of the combinations tried were irritating, but eventually one was found with tannic acid which was fairly satisfactory, as mentioned last year in my review⁵¹

This work was in progress when Hagedorn announced his discovery of protamine insulin Very soon afterward Bischoff⁶² found that histone obtained from thymus gland was effective in retarding the action of insulin The thymus histone precipitated insulin on the alkaline side of the iso-electric point for insulin The precipitate introduced intravenously produced a blood sugar response approximately the same as that of the original insulin, whereas when given intramuscularly it showed the retarded effect Diabetes in human beings was well controlled with it, and a "pooling effect" was noticeable after four or five days of daily injections Histone insulin in these respects behaves much as does protamine insulin Observations on it in 30 cases of diabetes have been reported by Gray, Bischoff and Sansum⁶³ No local or systemic reaction was noted, and an average of two and seven-tenths injections of unmodified insulin was reduced to an average of one and one-fifth injections a day

II NUTRITION

BY DR WILBUR

Advances in nutrition during the past year which may be of particular interest to clinicians have had to do chiefly with chemical and physiologic aspects of the vitamins It is becoming increasingly clear that such extensive pathologic changes as those which characterize marked states of vitamin deficiency are not common in this country, with the exception of those due to rickets and pellagra Consequently there is much interest in the possible frequency, nature and method of recognition of states of moderate and of mild deficiency of vitamins Such less marked states of deficiency depend principally on physiologic and perhaps slight pathologic changes in the tissues, and attempts are being made to develop satisfactory methods of measuring these

61 Maxwell, L. C. The Quantitative and Qualitative Ovarian Response to Distributed Dosage with Gonadotropic Extracts, *Am J Physiol* **110** 458-463 (Dec.) 1934

62 Bischoff, Fritz. Histone Combinations of the Protein Hormones, *Am J Physiol* **117** 182-187 (Sept.) 1936

63 Gray, P. A., Bischoff, Fritz, and Sansum, W. D. Treatment of Diabetes Mellitus with Insoluble Insulin Compounds, *Ann Int Med* **11** 274-284 (Aug.) 1937

physiologic disturbances in man and in experimental animals. The development of the biophotometric test for vitamin A deficiency and tolerance and saturation tests for vitamin C deficiency seem to be a step in this direction. As yet there is lack of evidence of the actual nutritional significance of slightly abnormal reactions to such tests.

The advances in the past year which were particularly worthy of note were the preparation of vitamin A in crystalline form, the designation of vitamin B₁ as thiamin chloride and of vitamin B₂, or G, as riboflavin by the Council on Pharmacy and Chemistry of the American Medical Association, the demonstration that "endemic" pellagra is the same disease as "secondary" pellagra, that it is due to dietary deficiency and that it responds to the same treatment as does "secondary" pellagra, that pellagra apparently responds promptly to treatment with nicotinic acid, and that vitamin C seems to be closely related to the phenomena of immunity, anaphylaxis and resistance to infection.

VITAMIN A

Vitamin A Requirement of Man—The daily requirement of vitamin A is still unknown. As stated in the review of last year,⁶⁴ it seems unlikely that the requirement of vitamin A or of any of the vitamins will be clearly established for many years. Variability in minimal and optimal requirements and in absorption, storage, utilization and destruction is sufficient under normal physiologic conditions to make it difficult to express in exact figures the requirements of any particular vitamin. However, information obtained within the past year by Jeghers⁶⁵ was to the effect that the minimal daily requirement for an adult is 4,000 U S P units of vitamin A. Jeans and his associates⁶⁶ noted that 3,000 U S P units of vitamin A daily were sufficient to meet the requirements of 2 boys aged 11 years as judged by photometric tests. These findings are in essential harmony with the recommendation of the Council on Pharmacy and Chemistry of the American Medical Association,⁶⁷ which has reiterated its previous stand of approving for advertising purposes cod liver oil which meets the standards given in "New and Nonofficial Remedies, 1936"—the dose of 2 teaspoonfuls daily should contain at least 6,250 and not over 10,000 U S P units of vitamin A.

64 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition, Arch Int Med **59** 512-555 (March) 1937.

65 Jeghers, Harold. The Degree and Prevalence of Vitamin A Deficiency in Adults, J A M A **109** 756-762 (Sept 4) 1937.

66 Jeans, P. C., Blanchard, Evelyn, and Zentmire, Zelma. Dark Adaptation and Vitamin A, J A M A **108** 451-458 (Feb 6) 1937.

67 The Dosage of Preparations Containing Vitamins A and D, report of the Council on Pharmacy and Chemistry, J A M A **109** 507 (Aug 14) 1937.

Attempts to determine the vitamin A requirement of cattle, sheep and swine led Guilbert, Miller and Hughes⁶⁸ to the conclusion that the minimum vitamin A requirement to prevent night blindness in these animals is from 6 to 8 micrograms of vitamin A (or 25 to 30 micrograms of carotene) for each kilogram of body weight. Crimm and Short⁶⁹ reported that the rate of utilization of vitamin A by the dog is between 157 and 300 U. S. P. units per kilogram of body weight per week.

Chemical Structure and Physiologic Activity—While the chemical structure and physiologic activity of vitamin A and its close relation to the yellow pigment carotene have been known for some time, the preparation of the vitamin in crystalline form from biologic material or by means of synthesis has been accomplished only in the past year. In January 1937 Holmes and Corbet⁷⁰ announced the preparation of a crystalline vitamin A concentrate from fish liver oil, and in October they⁷¹ reported that with the use of purified solvents, low temperatures and special technical procedures they had been able to obtain pale yellow crystals from three different fish oils. Determination of the molecular weight and elementary analysis of these crystals revealed a correspondence with the formula which had already been suggested for vitamin A. Bio-assay of the material indicated that it had a value of 3,000,000 U. S. P. units per gram. Synthesis of vitamin A has been reported by Fuson and Christ⁷² and by Kuhn and Morris⁷³. The latter workers found that their product was biologically active in daily doses of 0.8 microgram and that it agreed with respect to absorption spectrum and chromatographic behavior with natural vitamin A.

Little information has been added during the past year to the already recognized physiologic relation of vitamin A to epithelial tissues and to the visual purple of the rod cells of the retina. Stern and Salomon⁷⁴ as a result of their studies with ovo-verdin, a green pig-

68 Guilbert, H. R., Miller, R. F. and Hughes, E. H. The Minimum Vitamin A and Carotene Requirement of Cattle, Sheep and Swine. *J. Nutrition* **13** 543-564 (May) 1937.

69 Crimm, P. D., and Short, D. M. Vitamin A Deficiency in the Dog. *Am. J. Physiol.* **118** 477-482 (March) 1937.

70 Holmes, H. N. and Corbet, Ruth E. A Crystalline Vitamin A Concentrate. *Science* **85** 103 (Jan. 22) 1937.

71 Holmes, H. N., and Corbet, Ruth E. The Isolation of Crystalline Vitamin A. *J. Am. Chem. Soc.* **59** 2042-2047 (Oct.) 1937.

72 Fuson, R. C., and Christ, R. E. The Condensation of Beta-Cyclocitral with Dimethylacrolein. *Science* **84** 294-295 (Sept. 25) 1936.

73 Kuhn, R. and Morris, C. J. O. R. Synthese von Vitamin A. *Ber. d. deutsch. chem. Gesellsch.* **70** 853-858, 1937.

74 Stern, K. G., and Salomon, Kurt. Ovo-verdin, a Pigment Chemically Related to Visual Purple. *Science* **86** 310-311 (Oct. 1) 1937.

ment obtained from lobster eggs and apparently chemically related to visual purple, suggested that the rapidity of the regeneration of visual purple under physiologic conditions may be accounted for by the supposition that the primary step in the bleaching process of visual purple is not a denaturation of the protein carrier of the pigment but is perhaps a type of photodissociation like that of the reversible dissociation of ovaerdm. Further studies by Sure and Buchanan⁷⁵ of the antagonism of thyroxin and vitamins A and B indicated that vitamin A may not be as potent an antithyrogenic agent as is vitamin B.

Deficiency States—During the past year there has been much discussion of the incidence, methods of recognition and significance of vitamin A deficiency. It is clearly recognized that states of well developed vitamin A deficiency are uncommon in the United States, consequently, little dependence can be placed on purely clinical observations in the recognition of such deficiency states. Probably the principal reason for this is the fact that, as Jeghers⁶⁵ has pointed out, the worst diet which he encountered in clinical practice yielded 900 U S P units of vitamin A daily, and an intake of this amount would probably need to be continued for months or years in order to produce clinically important vitamin A deficiency. In an attempt to produce experimental evidence of vitamin A deficiency in man, Jeghers⁶⁵ took large doses of vitamin A and then reduced his intake to 200 U S P units daily. Within six days there was photometric evidence and in five weeks subjective evidence of night blindness. These abnormal findings disappeared within three days during which 100,000 units of vitamin A was consumed daily.

The earliest clinical manifestations of deficiency of vitamin A are related to the eyes and the skin. Jeghers⁷⁶ has pointed out that in his experience night blindness, in most instances not previously clearly recognized, has been a factor of considerable importance in causing difficulty in driving an automobile at night. He⁶⁵ reported that 12 per cent of a group of 162 medical students showed clinical manifestations of vitamin A deficiency, consisting, in order of frequency, of night blindness, photophobia, dryness of the skin, dryness of the conjunctivae, blepharitis and follicular hyperkeratosis.

Because of the infrequency of clinically recognizable vitamin A deficiency in the United States, efforts have been made by a variety of observers to develop satisfactory clinical or laboratory methods of determining the presence of states of partial or subclinical deficiency.

⁷⁵ Sure, Barnett, and Buchanan, Katharyn S. Influences of Hyperthyroidism on Vitamin A Reserves of the Albino Rat, *J. Nutrition* **13** 521-524 (May) 1937.

⁷⁶ Jeghers, Harold. Night Blindness Due to Vitamin A Deficiency. A Consideration of Its Importance in Traffic Problems. *New England J. Med.* **216** 51-56 (Jan 14) 1937.

of this vitamin. In general, such methods may be said to fall into two groups—clinical and pathologic. In the former group, in addition to clinical observations of symptoms of well defined deficiency states, such as those involving the eyes and the skin, may be considered examinations of the adaptation of the eyes to darkness, studies of the vitamin A content of the blood and urine, estimations of the “neutrophilic lag” and therapeutic trials with vitamin A in concentrated or crystalline form. Methods of study of pathologic material which may be helpful in the diagnosis include the histologic examination of tissue post mortem or at biopsy, estimations of the vitamin A content of the liver and other tissues and microscopic studies of cells scraped from the mucous membrane of the conjunctivae nose and female generative tract or of epithelial cells in the urine.

Since the popularization by Jeans and Zentmire⁷⁷ of the biophotometric method of studying the dark adaptation of the eyes as an index of vitamin A deficiency, numerous studies have been reported of the incidence of this deficiency in various groups of the population. While there may be some doubt as to the accuracy with which this method of examination measures the adequacy of the previous intake of vitamin A or is a measure of the degree of vitamin A deficiency, it seems obvious from the number of studies which have been made, from the comparative similarity of the results obtained and from the uniformly beneficial effects of administration of vitamin A concentrate for those who have shown abnormal results of the tests, that the results of such examinations are in some way influenced by the state of metabolism of vitamin A. For a discussion of the physiologic background and the value and technic of the biophotometric method of determining vitamin A deficiency, as well as of other methods of examining the eyes for the purpose of estimating the incidence and degree of this deficiency, one should consult the excellent review of Jeghers⁷⁸ or the paper of Maitra and Harris⁷⁹. Jeans and his associates⁶⁶ have modified the technic which they originally described and have concluded that the new photometer which they have developed reveals certain defects in the old test although the principles of the test are sound. While all these tests are subjective and demand a certain amount of intelligence

⁷⁷ Jeans, P. C., and Zentmire, Zelma. A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency. *J. A. M. A.* **102**: 892-895 (March 24) 1934.

⁷⁸ Jeghers, Harold. Night Blindness as a Criterion of Vitamin A Deficiency, *Ann. Int. Med.* **10**: 1304-1334 (March) 1937.

⁷⁹ Maitra, M. K. and Harris, L. J. Nutritional Surveys. Vitamin A Deficiency Among School Children in London and Cambridge, *Lancet* **2**: 1009-1014 (Oct. 30) 1937.

and cooperation on the part of the patient, Friderichsen and Edmund⁸⁰ have reported further studies of a method evolved by Friderichsen⁸¹ which is entirely objective and which can be utilized in examining infants. It depends on an estimation of the faintest amount of light which will provoke an oculomotor reflex. Further study should be made of this method, because with it subjective responses are eliminated.

In an effort to determine the state of vitamin A nutrition of patients, several investigators have made estimations of the vitamin A content of the blood and urine. These studies are not as yet sufficiently advanced to permit the development of significant conclusions. Methods of analysis which have been used have been principally modifications of the antimony trichloride test. Schneider and Weigand⁸² reported that vitamin A is not present in the urine of normal persons even when large doses are administered. However, they found that a large percentage of patients with cancer, tuberculosis and generalized infections eliminate the vitamin as a result of impairment of hepatic function or of a change in renal permeability. Boller, Brunner and Brodaty⁸³ also found that patients with hepatic and renal disease may eliminate vitamin A in the urine. Indeed, this finding was considered by them as of diagnostic value in these diseases and as always an extremely serious prognostic sign. Somewhat in contrast to these findings are those of Gaetgens⁸⁴ who observed traces of vitamin A in the urine of 8 of 39 pregnant women. After administration of concentrates of the vitamin to this group of women, larger amounts were eliminated, and the urine of 19 of 30 of these women gave positive results. The excretion of vitamin A did not seem to depend on an increase of the vitamin content of the blood.

The widespread pathologic changes which occur in tissues deprived of an adequate supply of vitamin A are fairly characteristic. Wolbach⁸⁵ has recently summarized these changes and has emphasized in

80 Friderichsen, C. and Edmund, C. Studies of Hypovitaminosis A. II. A New Method for Testing the Resorption of Vitamin A from Medicaments. *Am J Dis Child* **53** 89-109 (Jan.) 1937.

81 Friderichsen, C. Quantitative Investigations of the Resorption of A Vitamin in a Case of *Cochliakie*, *Acta pædiat* **18** 377-391, 1936.

82 Schneider, E. and Weigand, E. Pathological Elimination of Vitamin A in Urine, abstr., *J A M A* **108** 1927 (May 29) 1937.

83 Boller, R., Brunner, O., and Brodaty, E. Elimination of Vitamin A in the Urine, abstr., *J A M A* **109** 1162 (Oct. 2) 1937.

84 Gaetgens, G. Ueber die Ausscheidung von Vitamin A in der Gravidität. *Klin Wchnschr* **16** 52-53 (Jan. 9) 1937.

85 Wolbach, S. B. Vitamin Deficiency Experimentation as a Research Method in Biology, *Science* **86** 569-576 (Dec. 24) 1937, The Pathologic Changes Resulting from Vitamin A Deficiency, *J A M A* **108** 7-13 (Jan. 2) 1937.

particular the profound effect which is to be noted in epithelial tissues. Atrophy and subsequent keratinization of the epithelium are the typical changes observed. The diagnostic value of the presence of keratinized epithelium in scrapings from the conjunctivae and from the vaginal and nasal mucous membranes was mentioned in the review of last year.

Determination of the vitamin A content of the tissues post mortem has been reported to give considerable information in regard to vitamin A deficiency. Mooie⁸⁶ and Ellison and Moore⁸⁷ employed this method of examination in the analysis of the livers of 1,000 adults and of approximately 200 children less than 15 years of age. For adults the average value obtained in the 40 cases of accidental death was 220 U S P units per gram of moist tissue. For infants the average value was only 17 units. Such a wide fluctuation was found for the livers of normal persons that evaluation of the results obtained for the diseased livers was somewhat unsatisfactory. However, those diseases in which the reserves of vitamin A were above normal included thyroid diseases of all types and diabetes in adults and tuberculosis in children. Consistently low concentrations were observed for the livers of adults dying of nephritis, peritonitis, pneumonia, renal and vesical infections and other infectious diseases. The correct interpretation of these findings is not clear, because of the variety of factors which may influence vitamin A metabolism. However, Mooie⁸⁶ estimated that a human being with a normal vitamin A reserve in the liver could live for six months on a diet completely free from the vitamin and that the amount stored in the liver of the normal person is roughly equal to the amount secreted in breast milk during nine months of lactation.

The incidence of marked vitamin A deficiency in the United States is very small. The supposition that states of partial deficiency may be common is receiving continual emphasis as a result of studies with the biophotometer. For example, in his study of 162 medical students in Boston, Jegheis⁸⁸ found that 35 per cent of them had low photometric readings and that 12 per cent actually had clinical manifestations of deficiency. In a group of 149 subjects, including WPA workers, medical students, technicians and graduate nurses, all actively engaged in work and apparently healthy, he⁷⁸ found evidence to suggest that 34 per cent were deficient in vitamin A, while in a group of 103 ambulatory hospital patients convalescing from the usual type of diseases, only 33 per cent showed no evidence of deficiency. In Chicago Bai-

86 Moore, T. The Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem J* **31** 155-164 (Jan) 1937.

87 Ellison, J. B., and Moore, T. The Vitamin A Reserves of the Human Infant and Child in Health and Disease, *Biochem J* **31** 165-171 (Jan) 1937.

borka and Wasika,⁸⁸ using the biophotometric method of examination for 780 adults, reported that of 80 control subjects, 21 per cent gave evidence of borderline deficiency, while 4 per cent were actually deficient. Among clinic patients, 23 per cent gave evidence of borderline deficiency, and 60 per cent showed actual deficiency. That a close relation exists between the incidence of vitamin A deficiency as determined by the biophotometric test and the economic status of the person tested has been clearcut since the original report of Jeans and Zentmire⁷⁷ on the incidence of vitamin deficiency among the school children of Iowa. The studies cited indicate this also, as do those of Maitia and Harris⁷⁹ in England. The latter authors reported that among 200 elementary school children in the East of London and in Cambridge, between 22 and 36 per cent were in a category described as "definitely subnormal" in their reaction to the test, whereas in public schools (which correspond to private schools in the United States) none of the boys were definitely subnormal, and only 10 per cent were slightly below normal.

These studies all indicate that states of partial deficiency of vitamin A are more common among persons in the lower economic levels, who for financial reasons and ignorance regarding a proper diet may have an inadequate intake of food. Peculiarities in dietary habits, skipping of meals and poor choice of foods were recognized by Jeghers⁶⁵ as factors of great importance predisposing to the development of vitamin A deficiency even among an intelligent group of students.

What is the significance of these observations? Is it actually true that from 30 to 50 per cent or even more of our population receive an intake of vitamin A which is inadequate to meet the optimum physiologic needs? Is it necessary that an individual have a normal response to such a test as the biophotometric test in order to be considered perfectly healthy? These are questions of paramount importance in nutrition, but until much further information is available they cannot be satisfactorily answered.

The treatment of deficiency of vitamin A remains unchanged. Concentrates of the vitamin are available principally in the form of concentrated fish liver oils. Carotene is available as an active therapeutic agent, but larger doses of it than of the vitamin are needed to produce comparable results. A significant principle in the treatment of vitamin deficiency diseases is the use of massive doses of vitamins. Jeghers⁶⁵ has confirmed this by observing that the best results were obtained

88 Barborka, C. J., and Wasika, Paul. Vitamin A Deficiency. Results of Dark Adaptation Tests on Seven Hundred and Eighty Adults read by title before the Central Society for Clinical Research, Chicago, Nov. 5 and 6, 1937.

when 70,000 units daily of vitamin A was taken orally for two weeks followed by 25,000 units daily until dark adaptation returned to normal

The relation of vitamin A deficiency to the development of calculi in the urinary tract has been discussed in previous reviews. In the past year studies indicating that such a relation exists have been published by Feldman,⁸⁹ but the relation has been denied by Lassen and Olesen⁹⁰ and by Oppenheimer and Pollack.⁹¹

Because the metabolism of carotene has been closely identified with the function of the liver, Clark, Robinson and Schiff⁹² attempted to use this substance in testing hepatic function, but they concluded that the results were of no apparent value.

THE VITAMIN B COMPLEX

For the sake of convenience the components of the vitamin B complex will be considered as a group, although the individual constituents differ widely chemically and in their physiologic and therefore in their clinical behavior. Largely as a result of extensive chemical studies, including isolation and synthesis of some of the components and as a result of biologic research and a clearer understanding of terms, some of the preexisting confusion surrounding the components of the vitamin B complex is becoming clarified. In a recent review of this subject Nelson⁹³ designated the following components:

- 1 Vitamin B₁, the antiberiberi vitamin that prevents beriberi in man and polyneuritis in animals

- 2 Riboflavin, a compound necessary for growth in chicks and rats and for the prevention of cataracts in rats. It is a component of the oxidation-reduction system of living cells

- 3 P-P factor, a nutritional factor effective in the prevention of human pellagra

- 4 Filtrate factor, a factor for the prevention of a nutritional dermatosis in chicks. Concentrates which contain this factor have been shown to be effective in the treatment of human pellagra and black tongue in dogs

- 5 Vitamin B₆, a factor necessary for rapid gains in weight and normal nutrition of pigeons

⁸⁹ Feldman, J. B. Dark Adaptation as a Clinical Test. *Arch. Ophth.* **17**: 648-661 (April) 1937.

⁹⁰ Lassen, H. K., and Olesen, M. Significance of A. Avitaminosis and Hyperparathyroidism in the Formation of Urinary Calculi. *Hospitaltid.* **80**: 435-443 (April 20) 1937.

⁹¹ Oppenheimer, G. D. and Pollack, H. Attempted Solution of Renal Calculi by Dietetic Measures. *J. A. M. A.* **108**: 349-352 (Jan. 30) 1937.

⁹² Clark, B. B., Robinson, J. B., and Schiff, L. I. Concerning the Use of Carotene as a Liver Function Test. *Am. J. Physiol.* **119**: 288 (June) 1937.

⁹³ Nelson, E. M. The Components of the Vitamin B Complex, *J. A. M. A.*, to be published.

- 6 Vitamin B₂, a factor for the prevention of a specific paralysis in rats and chicks
- 7 Vitamin B₃, a factor necessary for the maintenance of weight in pigeons
- 8 Vitamin B₆, or vitamin H, a factor for the prevention of a nutritional dermatosis in rats
- 9 Factor W, a factor necessary for growth of rats

In another summary of the components of the vitamin B complex Elvehjem⁹⁴ listed six factors, namely, vitamin B₁, flavin, the antipellagra factor (B₂, or G), the 1st antidermatitis factor (B₆), the antiparalytic factor (B₄) and factor W (the alcohol-ether precipitate factor of Elvehjem, Koehn and Olesen)

Whether or not these "components" represent chemical entities required by certain species of animals and not by others is not clear. Fortunately for clinicians, much of the confusion surrounding this problem will probably vanish with the development of pure crystalline products and a less ambiguous nomenclature. So far only two members of the vitamin B complex, namely, vitamin B₁ and the P-P factor, have been unequivocally linked with deficiency disease in man.

Vitamin B₁ (Thiamin Chloride)—The Council on Pharmacy and Chemistry of the American Medical Association,⁹⁵ on the suggestion of R. R. Williams, decided to adopt the name thiamin chloride (bromide, sulfate and so on) as the common name for vitamin B₁, with the proviso that if the International Committee on Nomenclature in 1938 should adopt some other suitable name the Council will feel free to concur in the use of the international name, with thiamin chloride as a synonym. The American Society for Biological Chemists, the American Institute of Nutrition and the Committee on Nomenclature of the American Chemical Society have all tentatively approved the term thiamin, although the term aneurin, introduced by Jansen, of Amsterdam, who first isolated the substance, is widely used on the continent and in England.

Chemistry and Physiology—The chemical structure of thiamin chloride has been known for several years, and the substance has been synthesized and appears on the market principally in that form. Leong and Harris⁹⁶ have evidence that synthetic and natural crystalline vita-

94 Elvehjem, C. A. Vitamin B Fractions. Their Nomenclature and Functions, *J. Nutrition* (supp.) **13** 11-12 (June) 1937.

95 Thiamin Chloride, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **109** 952 (Sept. 18) 1937.

96 Leong, P. C., and Harris, L. J. Antineuritic Potency of Synthetic and Natural Crystalline Vitamin B₁ as Determined by the "Bradycardia Method," *Biochem. J.* **31** 672-680 (April) 1937.

min B₁ are equally potent, as determined by the bradycardia method, and that the antineuritic activity of 2.8 to 3 micrograms of the crystalline substance is equal to that of 1 international unit

It has long been recognized that the activity of thiamin is closely related to that of the oxidation of carbohydrate and particularly of pyruvic and perhaps lactic acid. In a recent excellent summary of the chemical properties of thiamin, Williams⁹⁷ pointed out that not only is it almost certain that the disposal of pyruvic acid by an enzymic decarboxylation is one of the functions of thiamin, but thiamin probably has other broad functions as well, suggesting that it is "one of nature's earlier and more fundamental inventions in the process of evolving life." Further evidence of the oxidative role of thiamin in metabolism is presented by Taylor, Weiss and Wilkins,⁹⁸ who found that the elevation of the content of bisulfite binding substances in the blood in certain cases of vitamin B₁ deficiency could not be explained entirely by the presence of acetone, of diacetic acid or of pyruvic acid. McHenry⁹⁹ presented a hypothesis suggesting that thiamin is necessary for the synthesis of fat from carbohydrate.

Requirements—The daily intake of thiamin in food by adults is probably in the neighborhood of 1 to 2 mg. This amount apparently satisfies the requirement of man for the substance, although, as calculated by Cowgill, the need varies with the weight and with the total metabolism of the organism. Cowgill¹⁰⁰ has recently assembled further data on the vitamin B₁ requirements of man. For infants the estimate of the desired intake was based on the amount in mother's milk, which with a maximum thiamin content would be about 80 U. S. P. units daily. The "American Public Yearbook, 1934-1935" recommends a minimum amount of 50 units daily. Cowgill¹⁰⁰ stated that for children the figure for optimum retention of thiamin is six to seven times the minimum which prevents beriberi. He stated that during pregnancy and lactation 10 units for each 100 calories per day is a safe amount to advise. Schlutz and Knott¹⁰¹ concluded that 20 units of vitamin B₁

97 Williams, R. R. The Chemistry of Thiamin (Vitamin B₁), J. A. M. A., to be published.

98 Taylor, F. H. L., Weiss, Soma, and Wilkins, R. W. The Bisulphite Binding Power of the Blood in Health and in Disease, with Special Reference to Vitamin B₁ Deficiency, J. Clin. Investigation **16** 833-843 (Nov.) 1937.

99 McHenry, E. W. Vitamin B₁ and the Synthesis of Fat from Carbohydrate, Science **86** 200 (Aug. 27) 1937.

100 Cowgill, G. R. Vitamin Requirements of Man, J. Nutrition (supp.) **13** 23-24 (June) 1937.

101 Schlutz, F. W., and Knott, E. M. The Vitamin B Requirement of Children. The Effects of Varied Ingestion of Vitamin B upon the Food Consumption of Children, J. Nutrition (supp.) **13** 13 (June) 1937.

for each kilogram of body weight may be taken tentatively as the optimum requirement for children. In a series of extensive studies Poole, Hamil, Cooley and Macy¹⁰² noted the effect on 193 normal full term infants over the course of one year of doses of thiamin 90 to 100 units (Sherman-Chase) higher than the doses given to an apparently normal control group. They said they felt justified in interpreting the findings as indicating "that increased amounts of vitamin B₁ in the diets of infants did aid in promoting a more stabilized growth and greater nutritional stability." That a wide margin exists between minimal and optimal levels of thiamin requirement is indicated by the work of Knott¹⁰³.

Deficiency States—Beriberi has been recognized as the classic example of thiamin deficiency in man, and the pathologic changes observed in this disease have been interpreted as evidence of changes characteristic of this deficiency. In summarizing his long experience with this phase of the disease, Vedder¹⁰⁴ pointed out that the three principal changes have to do with the cardiovascular system, the nervous system and anasarca. Death appears to be caused by cardiac hypertrophy followed by sudden dilatation and cardiac failure, and on postmortem examination the right side of the heart is markedly dilated and hypertrophied. Changes in the nervous system are characterized by degeneration of the myelin sheaths of nerve fibers, which is a constant feature and usually affects the majority of fibers. These degenerative changes involve the sympathetic as well as the somatic nervous system.

In the past year there have been numerous papers of interest regarding the clinical features of thiamin deficiency in man. Strauss¹⁰⁵ has summarized the present views on these states of deficiency by indicating that the nervous and circulatory systems are predominantly involved. The diagnoses of alcoholic, diabetic, biliary, gastrogenic and postinfectious polyneuritis, polyneuritis of pregnancy and the Korsakoff syndrome, he concluded, have all concealed the true diagnosis of thiamin deficiency. While symptoms of these conditions may be sudden in onset, they are generally insidious, and the earliest manifestations usually are heaviness of the legs and tenderness of the calf muscles when they are squeezed. Weakness of the limbs, burning of the soles

102 Poole, M. W., Hamil, B. M., Cooley, T. B., and Macy, I. G. Stabilizing Effect of Increased Vitamin B (B₁) Intake on Growth and Nutrition of Infants, *Am J Dis Child* **54** 726-749 (Oct.) 1937.

103 Knott, Elizabeth M. A Quantitative Study of the Utilization and Retention of Vitamin B by Young Children, *J Nutrition* **12** 597-611 (Dec.) 1936.

104 Vedder, E. B. The Pathology of Beriberi, *J A M A*, to be published.

105 Strauss, M. B. The Therapeutic Use of Vitamin B₁ in Polyneuritis and Cardiovascular Conditions, *J A M A*, to be published.

and numbness of the dorsum and lower part of the ankle are next to appear, followed by hypesthesia which advances up the leg and thigh and by atrophy of the muscles and of the skin. Similar changes occur in the upper extremities when they are involved. The differential diagnosis of this form of polyneuritis is usually not difficult, according to Strauss,¹⁰⁵ for in the polyneuritis due to poisoning from heavy metals particularly lead, the motor nerves and anterior horn cells of the spinal cord are primarily affected. Involvement of sensation is minimal, pain is rare and the upper extremities are more often affected in polyneuritis due to lead poisoning. The first symptoms of thiamin deficiency may appear in alcoholic addicts about twenty days after total absence of thiamin from the diet, according to the observations of Jolliffe, Colbert and Joffe.¹⁰⁶

The cardiovascular manifestations of thiamin deficiency have been extensively studied by Weiss and Wilkins¹⁰⁷ and consist principally of dyspnea and palpitation on exertion, tachycardia and edema. It is obvious that these manifestations do not, for the present at least, comprise a rigid and easily recognized clinical syndrome, and the diagnosis should not be made without additional evidence in the form of other clinical manifestations of thiamin deficiency, without a history of a grossly inadequate diet, without adequate response to treatment with thiamin or without the determination of certain technical measurements of the circulation. The last-mentioned evidence indicates that, whereas in other forms of congestive failure, except that of hyperthyroidism, there is conspicuous slowing of the circulation, in cases in which there are cardiovascular symptoms due to thiamin deficiency, there is an increase in both the circulation time and the circulatory minute volume.

Other manifestations of thiamin deficiency which have been reported over a period of years include gastro-intestinal changes, such as anorexia, glossitis, achlorhydria and diarrhea, and changes in the blood such as those indicating anemia. As Strauss¹⁰⁵ has pointed out, there is considerable evidence to suggest that these phenomena are at least in part, if not entirely, manifestations of a deficiency of some portion of the vitamin B complex other than thiamin. In this connection, the

106 Jolliffe, Norman, Colbert, C. N., and Joffe, P. M. Observations of the Etiological Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, *Am. J. M. Sc.* **191** 515-526 (April) 1936.

107 Weiss, Soma, and Wilkins, R. W. (a) The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, *Tr. A. Am. Physicians* **51** 341-373 1936, (b) The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), *Ann. Int. Med.* **11** 104-148 (July) 1937, (c) Disturbances of the Cardiovascular System in Nutritional Deficiency, *J. A. M. A.* **109** 786-793 (Sept. 4) 1937.

studies made by Joffe and Jolliffe¹⁰⁸ on the curves for gastric acidity of 105 chronic alcoholic addicts are of particular interest. These authors stated the opinion that an "achlorhydria preventive factor" may be a part of the vitamin B complex but that this factor is not identical with either thiamin or the pellagra-preventive factor. Sure and Harrelson¹⁰⁹ said they believed that they had conclusively demonstrated in rats that deficiency of the vitamin B complex or of vitamin B₁ associated with varying degrees of paralysis does not lead to any significant change in the rate of peptic digestion, suggesting that, in this species at least, deficiency of the vitamin B complex has no influence on this phase of gastro-intestinal function.

The factor causing the anemia commonly found in association with deficiency of the vitamin B complex has not been clearly established. There is evidence to suggest that it is closely related to the heat-stable portion of the complex known formerly as vitamin B₂ or G and now recognized as consisting of riboflavin, the pellagra-preventive factor and possibly other factors. A report of considerable interest from this standpoint is that of Elsom¹¹⁰ on the occurrence of macrocytic anemia in a group of pregnant women on a diet adequate in all respects except that in the latter months of pregnancy the intake of vitamin B (whole complex) did not equal that estimated to be adequate according to Cowgill's formula. In the first place, this study indicates clearly that calculations of vitamin B requirement by Cowgill's formula are of definite clinical value, that a characteristic anemia of the macrocytic type will develop in cases of deficiency of this complex and that symptoms involving the nervous and cardiovascular systems and the gastro-intestinal tract occur early in deficiency of the vitamin B complex. The early symptoms noted in these cases were paresthesias or impairment of vibratory sensation, susceptibility to fatigue, edema, tachycardia, and gastro-intestinal symptoms, consisting of anorexia, heartburn or a sense of constant fullness in the epigastrium, alterations of the tongue and constipation. Observations made by Elsom¹¹⁰ suggested that a diet that is adequate in vitamin B (complex) at the outset of pregnancy may fail to meet the increased demand for that vitamin complex late in pregnancy. Prompt response to the changes in the blood and other organs was obtained by the administration of yeast orally or of liver extract intramuscularly.

108 Joffe, P. M., and Jolliffe, Norman. The Gastric Acidity in Chronic Alcoholics, *Am J M Sc* **193** 501-510 (April) 1937.

109 Sure, Barnett, and Harrelson, R. T. Enzymic Efficiency in Avitaminosis VII. Peptic Digestion in Vitamin B Deficiency, *Am J Digest Dis & Nutrition* **4** 177-179 (May) 1937.

110 Elsom, Katherine O'S. Macrocytic Anemia in Pregnant Women with Vitamin B Deficiency, *J Clin Investigation* **16** 463-474 (May) 1937.

The possibility that thiamin may have some effect on bones, particularly in cases of gout, is voiced by Voihaus,¹¹¹ but confirmation will be needed before such a probability can be accepted as a fact.

The incidence of thiamin deficiency in the United States is unknown. While definitely recognizable beriberi is uncommon, there is some evidence to suggest that states of partial deficiency are not so infrequent. Weiss and Wilkins,^{107c} for instance, have reported observation on 120 patients in the Boston City Hospital with beriberi marked by cardiovascular as well as neurologic manifestations. Even more frequently patients are observed with "alcoholic" and other types of polyneuritis which are now recognized as being due to deficiency of thiamin.

Thiamin Therapy—The prevention of or treatment for states of thiamin deficiency demands the use of foods or of such substances as yeast and wheat germ which are rich sources of thiamin. Crystalline preparations are available for oral or parenteral administration. Daily intramuscular or intravenous injection of 20 to 50 mg. of crystalline thiamin is apparently an adequate therapeutic dose. Larger doses, as much as 90 to 100 mg., have been given without harmful effect. Molitor and Sampson,¹¹² in their studies of the effects of increased doses of natural and synthetic vitamin B₁ reported that in dogs the minimum dose of vitamin B₁ which is fatal on intravenous administration is 350 mg. per kilogram of body weight. A subcutaneous and oral dose of from six to forty times this amount is needed to produce fatal results, the symptoms of which are shock, muscular tremor, catatonic spasm and disturbed respiration followed by respiratory failure.

In addition to crystalline thiamin, Strauss¹⁰⁵ recommended the use of plain or autolyzed brewers' yeast as a convenient means of administering not only thiamin but other portions of the vitamin B complex. Thirty grams of powdered brewers' yeast of good potency administered three times daily or 6 Gm. of autolyzed brewers' yeast given three times daily is generally adequate in the treatment of patients only moderately ill with deficiency and without apparent abnormalities in gastrointestinal function which would interfere with absorption. In addition, dilute liver extracts, suitable for intramuscular injection, given in doses of 10 to 20 cc. or more daily, are helpful in controlling glossitis and cutaneous manifestations of the type associated with pellagra.

The result of efficient treatment of polyneuritis depends largely on the duration and the extent of the disease. In cases of acute involve-

111 Voihaus, M. G. cited by Stafford, J. The Effect of Vitamin B₁ on Bones, *Science* (supp.) **85** 10 (June 18) 1937.

112 Molitor, H., and Sampson, W. L. Effects of Increased Doses of Natural and Synthetic Vitamin B₁, *Nutrition Abstr. & Rev.* **7** 322 (Oct.) 1937.

ment there may be a complete remission of all signs and symptoms in a matter of weeks. However, in cases of advanced polyneuritis the response may be slow, a matter of many months, since it is dependent on regeneration of long nerve fibers. The response of cardiovascular symptoms is often remarkable and almost a matter of hours, although in cases of long-standing involvement, recovery may require several weeks of adequate treatment.

Because of the similarity in certain respects of thiamin deficiency in animals and sickness following roentgen treatment, Martin and Moursund¹¹³ tried the effect of thiamin in these cases, with striking clinical results. Popp¹¹⁴ has had a similar gratifying experience.

Methods of detecting thiamin deficiencies rest principally on the basis of the previously mentioned clinical changes and on the basis of their disappearance after thiamin therapy. However, certain objective methods of examination may prove useful. Those observers who are interested principally in experimental thiamin deficiency use such methods as the rate of growth in rats, fermentation tests, the bradycardia test and the thiochrome test, which depends on the oxidation of thiamin to thiochrome which is fluorescent. Meiklejohn¹¹⁵ has reported a method for estimating the thiamin content of the blood, and there have been several reports of methods of estimating the amount of thiamin in the urine. However, as yet these methods have not been useful as clinical procedures. In the group of cases of vitamin B deficiency reported by Elsom,¹¹⁶ Lewy¹¹⁶ noted some interesting chronaximetric changes in the radial nerves, which he found often preceded clinical and hematologic evidence of the deficiency. The degree of change in the peripheral nerves indicated by chronaximetric examination coincided with the severity of the clinical manifestations of deficiency, and improvement in the nerves was noted after vitamin B therapy.

All these methods are indirect and are based on biologic tests which necessarily subject them to some variation. Consequently, it is of great importance that chemical methods of assaying thiamin be developed. Williams⁹⁷ stated that it will be no easy matter to devise a satisfactory method of chemical assay for thiamin in foods, for, among other reasons, thiamin occurs in foods in the proportion of from one-

113 Martin, C. L., and Moursund, W. H., Jr. Treatment of Roentgen Sickness with Synthetic Vitamin B₁ HCl. Preliminary Report, *Am J Roentgenol* **38** 620-624 (Oct.) 1937.

114 Popp, W. C. Personal communication to the authors.

115 Meiklejohn, A. P. The Estimation of Vitamin B₁ in Blood by a Modification of Schopfer's Test, *Biochem J* **31** 1441-1451 (Sept.) 1937.

116 Lewy, F. H. Chronaximetric Examination in B Avitaminosis During Pregnancy, *J Clin Investigation* **16** 475-477 (May) 1937.

tenth to four parts per million, roughly, it is a thousand times less abundant than vitamin C, and it possesses no known physical property which is adapted to delicate testing. Prebluda and McCollum¹¹⁷ and more recently Naiman¹¹⁸ have suggested methods which may prove useful in the chemical assay of this substance.

Riboflavin (Vitamin B₂ or G, Lactoflavin)—The heat-stable portion of the vitamin B complex has been known principally as vitamin G in this country and as vitamin B₂ in England and on the Continent. In recent years it has been demonstrated clearly that this part of the vitamin B complex consists of several factors: a flavin, vitamin B₁, and another substance closely related to, if not in fact, the pellagra-preventive factor of Goldberger. For the flavin factor the term lactoflavin was originally adopted and appears widely in the literature, but in April 1937 the Council on Pharmacy and Chemistry¹¹⁹ adopted the term riboflavin for this substance to indicate that the compound is a ribose derivative of iso-alloxazine.

Riboflavin is a widely distributed yellow substance with a characteristic green fluorescence; it is found in animal and plant sources of food, particularly in the green leaves of actively growing plants. It is required by the rat for growth and for maintenance of health and probably also by other mammals, including man, although there has been described no specific disease in man due to riboflavin deficiency. Riboflavin has some function in the oxidative processes in cells and, according to Hogan,¹²⁰ is probably an essential constituent of the yellow oxidative enzyme that cannot be synthesized by the animal cell.

According to Hogan,¹²⁰ the flavin content of organs cannot be increased by administration of large doses of this substance. The body guards its store of riboflavin, although the latter is found in the urine as an excretory product when the diet is normal. Emmerie¹²¹ has estimated that the daily elimination of riboflavin in the urine of man is 819 to 1,250 micrograms. The rate of destruction of riboflavin in the body is unknown, but there is evidence to suggest that some destruction does occur.

117 Prebluda, H. P., and McCollum, E. V. A Chemical Reagent for the Detection and Estimation of Vitamin B₁, *Science* **84** 488 (Nov. 27) 1936.

118 Naiman, Barnett. A Reagent for Vitamin B₁, *Science* **85** 290 (March 19) 1937.

119 Riboflavin, the Accepted Name for Vitamin B₂, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **108** 1340-1341 (April 17) 1937.

120 Hogan, A. G. Riboflavin. Physiology and Pathology, *J. A. M. A.*, to be published.

121 Emmerie, A., cited by Hogan¹²⁰.

The daily requirement of riboflavin is unknown. Hogan¹²⁰ estimated from Emmerie's data that a man should receive from 2 to 3 mg of riboflavin daily.

The suggestion of Rose¹²² is that children up to 10 years of age should receive at least 400 units (Bourquin-Sherman) of riboflavin a day and that adults should receive 200 units daily for each 100 calories consumed. The figures of Rose and of Emmerie and those of Stiebling¹²³ are essentially in agreement, since Sherman and Lanford¹²⁴ estimated that the "Bourquin-Sherman unit" of vitamin G represents about 3 to 5 micrograms of riboflavin. Whether or not larger doses than these will lead to states of better nutrition cannot be judged at present, although, as Sherman¹²⁵ has pointed out in rats, the optimal intake of vitamin G (riboflavin) is much higher (probably at least fourfold) than the minimal requirement. Apparently overdoses of riboflavin are not toxic.

There has been much speculation in regard to the possible clinical role of riboflavin. States of deficiency of this substance have not been reported in man. Riboflavin has been reported to be ineffective in the treatment of pellagra in man, and evidently it is neither the intrinsic nor the extrinsic factor in pernicious anemia.

The Pellagra-Preventive Factor, Pellagra—The etiology of pellagra has been in dispute since the disease was first described. That a dietary factor may be significant has been realized for many years, and, despite important evidence to this effect which has been obtained in the past few years, many clinicians have been of the opinion that endemic pellagra of the South could not be explained solely on the basis of nutritional deficiency. Much confusion has been added to the problem because, as Sebiell¹²⁶ has pointed out, there are four postulated factors about which sufficient evidence exists to warrant discussion in connection with the prevention and treatment of pellagra. These are riboflavin, the rat antidermatitis factor, or vitamin B₆, the filtrate factor, or chicken pellagra factor, and the pellagra-preventive (P-P) vitamin, or black tongue-preventive factor.

It has been recognized since the work of Goldberger that the deficiency of a factor called the pellagra-preventive, or P-P, factor could

122 Rose, Marv S. Laboratory Handbook for Dietetics, ed 4, New York, The Macmillan Company, 1937.

123 Stiebling, Hazel K., cited by Sherman and Lanford¹⁻⁴.

124 Sherman, H. C., and Lanford, Caroline S. Riboflavin. Dietary Sources and Requirements, J. A. M. A., to be published.

125 Sherman, H. C., and Ellis, Lillian N. Necessary Versus Optimal Intake of Vitamin G, J. Biol. Chem. **104** 91-97 (Jan.) 1934.

126 Sebiell, W. H. Vitamins in Relation to the Prevention and Treatment of Pellagra, J. A. M. A., to be published.

be related etiologically to at least some cases of pellagra in man. Subsequently it was revealed that the P-P factor and the vitamin B complex are closely related. In the past year there have been two important observations which will probably be of great usefulness in leading to a solution of the problems of the etiology of pellagra and its relation to vitamin B deficiency. These have to do with the observations of Spies, Chinn and McLester,¹²⁷ who showed that endemic pellagra, like so-called alcoholic pellagra, responds to the administration of a high caloric and high protein diet, large amounts of yeast and good nursing care, and with the demonstration that nicotinic acid is effective in relieving the symptoms and signs of pellagra.

Spies and his co-workers¹²⁷ studied a series of 50 patients with severe endemic pellagra admitted to the hospital for treatment. Forty-seven of the patients recovered when given a high caloric and high protein diet, large amounts of a potent brewers' yeast and general symptomatic and supportive treatment, rest and good nursing care. Each of the 3 patients who died showed at that time healed or healing pellagrous lesions. The specific therapeutic agents used consisted of powdered brewers' yeast in daily quantities of 180 to 270 Gm (best given in doses of about 20 Gm each in iced milk) and intravenous injections of liver extract, 20 cc four or five times daily. The study of these cases seems to indicate clearly that endemic and alcoholic pellagra have the same clinical symptoms and similar lesions and that they respond to the same treatment. They are in fact the same syndrome and constitute a clearly defined deficiency disease. This is an important observation and is of much more than academic interest, for, as Musser¹²⁸ has recently stated

It is absolutely astounding that statements are made in which it is said that pellagra is rapidly disappearing from the country. Pellagra, according to the United States Public Health Service statistics for 1930, caused more deaths than all the diseases listed as communicable except pneumonia, tuberculosis and influenza.

Perhaps of greater interest and importance are observations of the effect of nicotinic acid in cases of pellagra. Elvehjem and his associates¹²⁹ isolated nicotinic acid amide from active concentrates of liver extract and discovered that it, as well as a synthetic preparation of nicotinic acid, was highly effective therapeutically in curing black tongue in dogs. Experiences with it in cases of pellagra in man have been

127 Spies, T. D., Chinn, A. B., and McLester, J. B. Severe Endemic Pellagra, *J. A. M. A.* **108** 853-857 (March 13) 1937, Treatment of Endemic Pellagra. *South. M. J.* **30** 18-23 (Jan.) 1937.

128 Musser, J. H., cited in The Treatment of Pellagra editorial, *J. A. M. A.* **108** 974 (March 20) 1937.

129 Elvehjem, C. A., Madden, R. J., Strong, F. M., and Wooley, D. W. Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue. *J. Am. Chem. Soc.* **59** 1767 (Sept.) 1937.

highly successful Spies, Cooper and Blankenhorn¹³⁰ have reported the successful use of nicotinic acid by pellagrins in improving and healing the fiery red pellagrous dermatitis, glossitis, stomatitis and vaginitis with nicotinic acid. Since that time Spies¹³¹ has treated 6 additional pellagrins, with excellent results. Smith, Ruffin and Smith¹³² have also reported the case of a patient with endemic pellagra who made a dramatic recovery after the administration of nicotinic acid in doses of 60 mg daily for twelve days. The drug was given intravenously, intramuscularly and orally, and the cost of the total amount administered was only 10 cents.

In some studies reported earlier in the year Ruffin and Smith¹³³ noted the potency of various liver extracts in the treatment of pellagra. They observed that parenteral administration of liver extract results in subjective improvement of pellagrins but that complete healing of all the phases of the disease will not occur with this method of treatment and that relapse may follow exposure to sunshine. However, a previously ineffective dose of "residue" (what is left of the liver after extraction), in addition to partially effective parenteral treatment with liver extract, results in complete recovery. These findings suggested to Ruffin and Smith that the pellagra-preventive factor is composed of two substances. However, since the studies of nicotinic acid have been reported, it seems reasonable to speculate that nicotinic acid and the pellagra-preventive factor of Goldberger are closely related, if not identical.

The daily requirement of the pellagra-preventive factor is unknown. The pellagra-preventive values of various foodstuffs are tabulated in the paper by Sebrell,¹²⁶ including values principally for meat, butter-milk, collards, kale, green peas, tomatoes and tomato juice, turnip greens, wheat germ and yeast.

There is still considerable interest in the relation of sunlight to the cutaneous lesions of pellagra. According to Sebiell,¹²⁶ who has recently reviewed the evidence on this subject, sunlight in this disease is to be regarded as an irritant. Smith and Ruffin¹³⁴ reported that from statis-

130 Spies, T. D., Cooper, Clark, and Blankenhorn, M. A. A Note on the Administration of Nicotinic Acid to Pellagrins, read before the Central Society for Clinical Research, Chicago, Nov 5, 1937, abstr., J. A. M. A., to be published.

131 Spies, T. D. Personal communication to the author.

132 Smith, D. T., Ruffin, J. M., and Smith, Susan G. Pellagra Successfully Treated with Nicotinic Acid. A Case Report, J. A. M. A. **109** 2054-2055 (Dec 18) 1937.

133 Ruffin, J. M., and Smith, D. T. A Clinical Evaluation of the Potency of Various Extracts of Liver in the Treatment of Pellagra, South M. J. **30** 4-14 (Jan) 1937.

134 Smith, D. T., and Ruffin, J. M. Effect of Sunlight on Clinical Manifestations of Pellagra, Arch. Int. Med. **59** 631-645 (April) 1937.

tical and experimental observations it is concluded that exposure to sunlight of a susceptible subject who has been subsisting on a deficient diet precipitates the acute cutaneous manifestations of pellagra. Beckh, Ellinger and Spies¹³⁵ noted that the amount of porphyrins excreted in the urine of alcoholic pellagrins was usually increased above that of normal persons and that the increase bore a rough relation to the intensity of the lesions of the skin and mucous membranes.

The diagnosis of pellagra still rests on clinical ground. While cutaneous lesions and gastro-intestinal and nervous symptoms are usually present in cases of well advanced pellagra and are characteristic of the disease, it is important to remember that all these systems are not necessarily involved in every case, particularly early in the course of the disease. Spies and Cooper¹³⁶ have recently presented an excellent summary of the diagnostic features of pellagra and have emphasized the extreme variability of the symptomatology of the early stage of the disease.

Other Components of the Vitamin B Complex—Nelson⁹³ has aptly termed this group the "intangible members" of the vitamin B complex. The evidence of the existence of these factors has largely been obtained by such chemical methods as separation effected by selective adsorption and differences in stability to heat in solutions containing varying proportions of acid and alkali, and by such biologic methods as the responses of rats, pigeons and growing chicks fed diets of various types. Whether any of the factors listed earlier in this review are of significance in the nutrition of man is uncertain. Up to the present deficiency diseases in man resulting from their absence from the diet have not been reported.

VITAMIN C

Of considerable interest to clinicians have been recent studies of the relation of vitamin C to infectious diseases, to immune and anaphylactic phenomena and to hemorrhagic conditions.

Hemorrhage is one of the outstanding clinical features of scurvy and there has been much discussion of the possible etiologic role of vitamin C subnutrition in a variety of acute and chronic hemorrhagic states. Some clinicians have been inclined to feel that vitamin C subnutrition may be a significant factor in predisposing to hemorrhage and Rivers and Carlson¹³⁷ in their studies of a group of patients with

135 Beckh, W., Ellinger, P., and Spies, T. D. Porphyrinuria in Pellagra. *Quart J Med* 6 305-319 (July) 1937.

136 Spies, T. D., and Cooper, Clark. The Diagnosis of Pellagra, *Internat Clin* 4 1-11 (Dec) 1937.

137 Rivers, A. B., and Carlson, L. A. Vitamin C as a Supplement in the Therapy of Peptic Ulcer. Preliminary Report. *Proc Staff Meet, Mayo Clin* 12 383-384 (June 16) 1937.

peptic ulcer noted that in cases in which hemorrhage had occurred, the cevitamic acid content of the blood and urine was less than normal. The response to treatment with cevitamic acid was rapid and complete. Rivers and Carlson pointed out that the usual diets given to patients with peptic ulcer are likely to be deficient in vitamin C and that deficiency of the vitamin may play a conspicuous role in the etiology of hemorrhagic gastroduodenal lesions. Similarly, Lazarus¹³⁸ in his studies of 15 cases of peptic ulcer with bleeding, found 13 cases in which evidence of vitamin C subnutrition was present, in 3 cases in which hemorrhage did not occur, the amount of vitamin C excreted in the urine was low also.

In discussing this problem Finkle¹³⁹ pointed out that a fairly large proportion of the population suffers from an undersaturation of vitamin C and that there is as yet no evidence to justify the conclusion that vitamin C deficiency has a causal relation to any pathologic condition other than scurvy. Until this problem can be finally settled, perhaps the most reasonable view to take is that while treatment of hemorrhagic conditions with vitamin C should not be carried out with unlimited hope, nevertheless it seems reasonable to advise the use of the vitamin therapeutically in many cases of bleeding. This view is taken because of the ease of administration of the substance and because by so doing at least one possible, even if uncertain, factor which predisposes to or perhaps increases the hemorrhagic tendency can be simply, rapidly and adequately controlled.

Most patients with infections require vitamin C in larger than usual quantities if normal levels are to be maintained in the blood and if normal quantities are to be excreted in the urine. Faulkner and Taylor¹⁴⁰ have indicated that serum levels for cevitamic acid of patients with infections are usually well below those of normal persons. They found that the amount of vitamin C needed to bring the levels of the serum and the urinary output to normal (serum, 0.7 mg per hundred cubic centimeters, urinary output, 15 to 20 mg in twenty-four hours) is far greater in the presence of infection than under normal conditions. One patient with active tuberculosis whom they observed required more than 200 mg of cevitamic acid daily to maintain a normal serum value and a normal urinary output.

138 Lazarus, Samuel. Vitamin C Nutrition in Cases of Haematemesis and Melaena, *Brit M J* **2** 1011-1015 (Nov. 20) 1937.

139 Finkle, Philip. Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, *J Clin Investigation* **16** 587-593 (July) 1937.

140 Faulkner, J. M., and Taylor, F. H. L. Vitamin C and Infections. *Ann Int Med* **10** 1867-1873 (June) 1937.

There has been much speculation as to the role which vitamin C may play in infectious diseases, particularly in regard to the possibility that a state of partial vitamin C deficiency may predispose to the development of an infection and that vitamin C has definite influences on the mechanisms of resistance to infection, including a significant action on the function of the cortex of the adrenal gland. Perla and Marmorston¹⁴¹ recently reviewed much of the experimental evidence and some of the clinical observations which have been made in this respect and have been able to report certain interesting conclusions. They observed that the influence of vitamin C on resistance to infection is dependent in part on its importance in the production of intercellular cement substance and that because of "the wide distribution of vitamin C in the body, its chemical properties and its influence on tissue respiration, it is suggested that its role in natural resistance to infection is dependent on its physiological importance in the oxidation-reduction process in cellular metabolism." The physiologic and pathologic alterations are expressed clinically by the drop which occurs in natural resistance to spontaneous and induced bacterial infection in the scorbutic state, even though the production of natural or immune antibodies is unaffected (except possibly that of opsonins).

However, in a recently published article, Jusatz¹⁴² reported finding that cevitamic acid under certain conditions is a stimulant to the production of specific antibodies. In rabbits stunted by a diet free from vitamins, he found a reduction in the normal bactericidal titer in the blood serum and a 90 per cent reduction in the power to form specific antibodies. With the administration of vitamins A, B, C and D separately, disappointing results were obtained, since there was no appreciable effect on the ability of the rabbits to produce antibodies. However, when these stunted rabbits were given an intravenous injection of a massive dose of cevitamic acid (33 to 66 mg.), there was a transient rise in the normal (or subnormal) bactericidal index. When the intravenous dose of vitamin C was increased to from 200 to 500 mg., a tripling of bactericidal power could be demonstrated as late as twenty-four hours after the injection, followed by a subsequent fall to the initial titer well before the sixth day. In subsequent studies Jusatz¹⁴² simplified his technique by adding 100 mg. of cevitamic acid to each immunizing dose of horse protein, with the result that an

141 Perla, D., and Marmorston, I. Role of Vitamin C in Resistance. *Arch Path* **23** 543-575 (April), 683-712 (May) 1937.

142 Jusatz, H. J., cited in *Cevitamic Acid Stimulation of Specific Antibody Production*, editorial, *J. A. M. A.* **109** 714-715 (Aug. 28) 1937.

average augmentation of fivefold to sevenfold in the production of specific antibodies was noted in the stunted rabbits

In their discussion of the role of vitamin C subnutrition in tuberculosis and rheumatic infection conditions in which there has been widespread clinical interest, Perla and Marmorston¹⁴¹ stated that it has not been unequivocally established "what effect chronic insufficiency of vitamin C in the diet has on natural resistance to a subsequently induced chronic infection such as tuberculosis" and that "it is suggested that undernutrition of vitamin C lowers the natural resistance of man to rheumatic infection and that such a nutritional factor may play a significant etiologic role in this disease" Fundamentally, therefore, the importance of vitamin C in resistance is secondary to its essential role in the maintenance of normal metabolism

Several papers have been published on studies of vitamin C metabolism in tuberculosis Abbasy, Harris and Ellman¹⁴³ reported a marked lowering of vitamin C excretion in tuberculosis and found that a definite correlation exists between the severity of the tuberculosis judged by usual clinical standards, and the diminution in urinary titer Martin and Heise¹⁴⁴ made similar observations and concluded that the responsible factors may be an abnormal chemical response of the gastrointestinal tract and an increased requirement of the tissues for vitamin C These workers received the impression that giving vitamin C improves the prognosis but emphasized that this was only an impression

Rinehart and his associates¹⁴⁵ have presented further studies of vitamin C in chronic infections, particularly in rheumatic fever and in certain cases of chronic rheumatoid or infectious arthritis According to their belief, vitamin C deficiency may be a significant factor in the etiology of the two last-mentioned conditions, and the deficiency is the result of a poor intake of vitamin C, anorexia and the digestive disturbances and intoxications of the disease The studies revealed that the vitamin C values for the blood of patients with rheumatic fever were considerably lower than those for patients with miscellaneous infections Discussion continues among experts on nutrition and rheumatism as to whether or not the low vitamin C level of the blood of these patients is a matter of cause or effect of the rheumatic disease

143 Abbasy, M A , Harris L J , and Ellman Philip Vitamin C and Infection Excretion of Vitamin C in Pulmonary Tuberculosis and in Rheumatoid Arthritis, *Lancet* **2** 181-183 (July 24) 1937

144 Martin, G J , and Heise, F H Vitamin C Nutrition in Pulmonary Tuberculosis, *Am J Digest Dis & Nutrition* **4** 368-374 (Aug) 1937

145 Rinehart, J F , Greenberg, L D , Baker, Frances, and Choy, F Vitamin C in Rheumatic Fever and Rheumatoid Arthritis, abstr, *J A M A* **109** 1394-1396 (Oct 23) 1937

A close relation between vitamin C and other types of infection has been reported in diphtheria by Kumagai,¹⁴⁶ in osteomyelitis by Abbasy, Harris and Hill¹⁴⁷ and in whooping cough by Ormerod, Unkauf and White¹⁴⁸. Kumagai¹⁴⁶ reported that he was able to reduce the mortality of necrotic diphtheria from 50 per cent to 30 per cent by the intravenous administration of 400 to 600 mg of vitamin C daily (along with dextrose and epinephrine). Abbasy and his associates found a diminished rate of excretion of vitamin C in the urine of patients with chronic osteomyelitis and a lowered response to a test dose of the substance, indicative of an apparently increased use of the vitamin. Ormerod and his co-workers discovered varying degrees of hypovitaminosis C in whooping cough and said they believed that they were able to decrease markedly the intensity, number and duration of the characteristic symptoms by saturating each patient with vitamin C.

In summarizing their observations on the relation of vitamin C to infections, Abbasy, Harris and Ellman¹⁴⁸ stated that "it is suggested that determination of the vitamin C excretion under controlled conditions may be of use as an index to confirm the presence of an infective state, and also as a prognostic sign to indicate the apparent activity of the disease."

Vitamin C may play a significant role also in anaphylactic reactions, for Lemke¹⁴⁹ demonstrated that the daily administration of vitamin C to guinea-pigs sensitized with horse or sheep serum resulted in the survival of the animals after the reinjection of a dose several times as large as an otherwise fatal dose. Sensitization as well as shock could be inhibited by a single parenteral injection of vitamin C thirty minutes before sensitization or a reinjection was given. The practical application of this observation was demonstrated by Lemke¹⁵⁰. The serum rash in children with diphtheria who were given 1 cc of horse serum per kilogram of body weight he was able to reduce considerably by administering 100 to 200 mg of cevitamic acid by mouth, beginning on the day of the injection.

146 Kumagai, K, cited in Action of Vitamin C in Diphtheria, Foreign Letter, J A M A **109** 601 (Aug 21) 1937

147 Abbasy, M A, Harris, L J, and Hill, N G. Vitamin C and Infection. Excretion of Vitamin C in Osteomyelitis, Lancet **2** 177-180 (July 24) 1937

148 Ormerod, M J, Unkauf, B M, and White, F D. A Further Report on the Ascorbic Acid Treatment of Whooping Cough, Canad M A J **37**:268-272 (Sept) 1937

149 Lemke, H. Modification of Anaphylactic Shock of Guinea Pigs by Vitamin C, abstr, J A M A **108** 604 (Feb 13) 1937

150 Lemke, H. Beeinflussung des anaphylaktischen Shocks der Meerschweinchen durch C-Vitamin, Nutrition Abstr & Rev **7** 346-347 (Oct) 1937

Determinations of Vitamin C in the Blood and Urine—PiJoan and Klemperer¹⁵¹ have advocated the use of potassium cyanide for preservation of the blood to prevent the loss of ascorbic acid by oxidation when assays are made by titration with 2,6-dichlorophenolindophenol. Blood is collected in tubes containing 5 mg of potassium cyanide and 10 mg of potassium oxalate. Speculation that acetylsalicylic acid might influence the urinary content of vitamin C has been denied by Youmans, Corlette, Frank and Corlette¹⁵². They were unable to demonstrate an increase in the content of vitamin C or of other reducing substances after the injection of 10 to 40 grains (0.65 to 2.6 Gm.) of acetylsalicylic acid.

Because various factors may influence the absorption of vitamin C from the intestine and may therefore interfere with saturation or tolerance tests, Finkle¹³⁹ and Wright, Lilienfeld and MacLenathen¹⁵³ have advocated the use of intravenously administered test doses. Finkle¹³⁹ used a test dose of 100 mg, and in normal persons he observed a rise in the vitamin C output of the urine within two to three hours after the injection to an average of about five times the preinjection level (0.03 to 0.05 mg per cubic centimeter of urine, or 13 to 20 mg in twenty-four hours). Finkle¹³⁹ concluded that with this technic the measurement of the total urinary excretion of vitamin C for about an eight hour period during the day, including an approximately six hour period after the intravenous injection, suffices to give a true indication of the state of saturation of the body with vitamin C. Wright and his associates¹⁵³ used a much larger intravenous test dose—1,000 mg—and reported that normally 500 mg or more of the 1,000 mg test dose is excreted in the urine during the first twenty-four hours and that 400 mg or more (80 per cent) of this is excreted in the first five hours after the injection. If such a method of intravenous administration of vitamin C proves reliable in determining the state of vitamin C nutrition, it should prove exceedingly useful in the future, because it is relatively simple, it can be carried out in a short time and it is without much source of error.

Clinical Studies—Intravenously administered test doses of vitamin C have among other advantages that of avoiding influences which may interfere with absorption of vitamin C. That achlorhydria may be such

151 PiJoan, M., and Klemperer, F. Determination of Blood Ascorbic Acid, *J. Clin. Investigation* **16** 443-445 (May) 1937.

152 Youmans, J. B., Corlette, M. D., Frank, H., and Corlette, M. Failure of Acetylsalicylic Acid to Effect Excretion of Ascorbic Acid (Vitamin C) in Urine, *Proc. Soc. Exper. Biol. & Med.* **36** 73-76 (Feb.) 1937.

153 Wright, I. S., Lilienfeld, Alfred, and MacLenathen, Elizabeth. Determination of Vitamin C Saturation—A Five Hour Test After an Intravenous Test Dose, *Arch. Int. Med.* **60** 264-271 (Aug.) 1937.

an influence is suggested by the work of Alt, Chinn and Farmer,¹⁵⁴ who measured the cevitic acid content of the blood of 49 patients with achlorhydria (mostly with pernicious anemia) and found that the mean value was 0.57 ± 0.02 mg for each hundred cubic centimeters, as compared with a level of 0.79 ± 0.03 mg for 29 normal or control subjects. Another interesting observation suggesting interference with intestinal absorption of vitamin C was that of Hagmann,¹⁵⁵ who recorded a case of active scurvy in a child $3\frac{1}{2}$ months old who was receiving 4 ounces (120 cc) of orange juice daily. The symptoms were completely relieved after treatment with vitamin C intravenously, and the child remained well subsequently when orange juice was given by mouth.

A possibly significant role of scurvy in the etiology of chronic subdural hematoma has been raised by Ingalls.¹⁵⁶ In 5 of the 9 cases he observed, roentgenograms of the bones were made, and in 3 cases there were changes characteristic of scurvy of the long bones.

The use of vitamin C as a therapeutic agent in several miscellaneous conditions has been reported recently. Volpe¹⁵⁷ has reported remarkable results following treatment with vitamin C of several patients with intractable psoriasis. Hirata and Suzuki¹⁵⁸ concluded that vitamin C in large doses was definitely helpful in 10 cases of progressive muscular dystrophy.

VITAMIN D

Biochemists have found a fertile field in their studies of sterol derivatives having vitamin D activity. In fact, Bills¹⁵⁹ has recently pointed out that the properties of vitamin D are exhibited by at least ten different sterol derivatives. Two of these are known to be of prime importance in medicine, namely, activated ergosterol and activated 7-dehydrocholesterol. The vitamin D of viosterol, irradiated yeast and yeast milk is identical and consists of activated ergosterol or calciferol. On the other hand, 7-dehydrocholesterol appears to be the principal activatable sterol or provitamin in cholesterol, the chief sterol of animal fats. It therefore comprises the vitamin D present in irradiated milk.

154 Alt, H. L., Chinn, Herman, and Farmer, C. J. The Blood Cevitic Acid in Patients with Achlorhydria, read before the Central Society for Clinical Research, Chicago, Nov. 5, 1937.

155 Hagmann, E. A. Active Scurvy in an Infant Receiving Orange Juice, *J. Pediat.* **11** 480-483 (Oct.) 1937.

156 Ingalls, T. H. The Role of Scurvy in the Etiology of Chronic Subdural Hematoma, *New England J. Med.* **215** 1279-1281 (Dec. 31) 1936.

157 Volpe, I. Ueber mehrere Erfolge in der Psoriasis. Behandlung mit Vitamin C, *Schweiz. med. Wchnschr.* **67** 498-499, 137.

158 Hirata, Y., and Suzuki, K. Progressive Muscular Dystrophy and Vitamin C, *Klin. Wchnschr.* **16** 1019 (July 17) 1937.

159 Bills, C. E. The Chemistry of Vitamin D, *J. A. M. A.*, to be published.

It is produced in the skin on exposure to ultraviolet light, and it is probably the chief, although not the only, form of vitamin D in fish oils. Bills¹⁵⁹ stated that a few of the other forms of vitamin D may have some practical significance, although most of them are of theoretic interest.

Because of the confusion which has existed in regard to the value of various types of milk and other food fortified with vitamin D, the Council on Foods recently reviewed¹⁶⁰ the present status of vitamin D milk. The conclusion which was reached should be helpful to practicing physicians. The Council made the decision that, for the present, milk is the only common food which will be considered for acceptance when fortified with vitamin D. The properties of vitamin D may be imparted to milk by irradiation of the milk, by proper feeding of vitamin D preparations to cows and by direct addition to milk of either natural or manufactured vitamin D concentrates. For those who may be interested in the types of vitamin D milk acceptable to the Council and in the use of vitamin D milk as a food for infants, children and adults, as well as in the requirements and allowable claims for vitamin D milk, reference should be made to this summary by the Council.¹⁶⁰

Investigators who have studied the problem of rickets and vitamin D deficiency include Hood and Ravitch,¹⁶¹ who, using irradiated cholesterol in doses of 400 to 775 U. S. P. units of vitamin D, found that as a preventive of rickets it was equal and perhaps superior, unit for unit, to viosterol or cod liver oil. Davidson, Merritt and Chipman¹⁶² found that irradiated evaporated milk was considerably less efficacious for the protection of the premature infant against rickets than was metabolized vitamin D milk when given under identical conditions. This was probably due to the smaller concentration of vitamin D units in the irradiated evaporated milk. Full term infants were practically completely protected from rickets with irradiated evaporated milk.

In their extensive experience with viosterol in the prevention and treatment of rickets, Shelling and Hopper¹⁶³ reported, as noted in the previous review,⁶⁴ that they did not encounter total refractoriness

160 The Present Status of Vitamin D Milk, report of Council on Foods, J. A. M. A. **108** 206-207 (Jan 16) 1937

161 Hood, J. S., and Ravitch, Irene. The Antirachitic Efficacy of Irradiated Cholesterol, J. Pediat. **11** 521-539 (Oct.) 1937

162 Davidson, L. T., Merritt, K. K., and Chipman, S. S. Prophylaxis of Rickets in Infants with Irradiated Evaporated Milk, Am. J. Dis. Child. **53** 1-21 (Jan.) 1937

163 Shelling, D. H., and Hopper, Katherine B. Calcium and Phosphorus Studies. XII Six Years' Clinical Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany and Allied Disorders, Bull. Johns Hopkins Hosp. **58** 137-211 (March) 1936

to viosterol, and partial refractoriness was noted in 1 case only. Consequently there is considerable interest in the report by Albright, Butler and Bloomberg¹⁶⁴ of a case of rickets resistant to vitamin D therapy. The patient, a boy of 16, had had rickets since the age of 1 year. There was chemical and microscopic evidence of rickets associated with secondary hyperparathyroidism. Failure of the rickets to heal was not due to interference with absorption, since vitamin D given intravenously and by irradiation did not help. However, when massive doses, namely, 150,000 to 1,500,000 U. S. P. units, were given daily by mouth, the disorder was corrected, and healing occurred. Albright and his associates interpreted this case as one due to intrinsic resistance to the antirachitic action of vitamin D.

That disease of the liver may be a factor in the "intrinsic resistance" to the antirachitic effectiveness of vitamin D is suggested by the work of Heymann.¹⁶⁵ After producing hepatic injury in rats by ligating the common bile duct or by intramuscular injections of carbon tetrachloride, he observed that in the former group from ten to twelve times and in the latter group from two to three times as much vitamin D was needed to cure experimental rickets as in a control group. This was not due to alteration in intestinal absorption, because the vitamin was given parenterally, nor was it the result of functional impairment of the osteogenic cells caused by jaundice. The evidence presented by Heymann seems to indicate that normal hepatic function is necessary for the normal metabolism of vitamin D.

It has been presumed for some time that among other functions of vitamin D is that of aiding the absorption of calcium from the intestine. In a recent study of the absorption and excretion of calcium and phosphorus of a patient after ileostomy and colostomy, Johnson¹⁶⁶ reported that no evidence was obtained to indicate that viosterol, in doses of 3 cc. three times a day, had any specific effect on the absorption of calcium from the intestine of an adult.

The rate of individual susceptibility to rickets has not been adequately studied. That in this, as well as in other deficiency diseases, hereditary influences may play a part is suggested by the studies of Streeter, Park and Jackson,¹⁶⁷ who were able by selection and inbreeding to develop

164 Albright, Fuller, Butler, A. M., and Bloomberg, Esther. Rickets Resistant to Vitamin D Therapy, *Am J Dis Child* **54** 529-547 (Sept.) 1937.

165 Heymann, Walter. Importance of the Liver for the Anti-Rachitic Efficacy of Vitamin D, *Proc Soc Exper Biol & Med* **36** 812-814 (June) 1937.

166 Johnson, R. M. The Absorption and Excretion of Calcium and Phosphorus in Three Patients with Colostomy and Ileostomy, *J Clin Investigation* **16** 223-230 (March) 1937.

167 Streeter, G. L., Park, E. A., and Jackson, Deborah. Hereditary Vulnerability to Dietary Defects in the Development of Bone, *Science* **85** 437 (May 7) 1937.

two strains of rats that to all appearances were alike save that one of them reacted more severely to a rachitic diet (vitamin D-free, high calcium and low phosphate diet) than did the other strain

Intoxication with Vitamin D—Because of the frequent use of massive doses of vitamin D in the treatment of chronic arthritis, hay fever, asthma, pulmonary tuberculosis and other conditions, much interest is attached to the possible toxic effect of such large doses. Steck, Deutsch, Reed and Struck¹⁶⁸ recently reported observations made on 64 dogs and 773 persons who had received massive doses of vitamin D. They concluded that "both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication." They added that hypervitaminosis D first produces cell injury, followed by deposition of calcium, but that the process is reversible and repairable if administration is discontinued promptly. Any suggestion of renal dysfunction is considered by them to be a definite contraindication, as is probably also arteriosclerosis, to the use of excessive doses of vitamin D.

Alleged Decalcifying Effect of Cereals—One of the most disturbing factors in nutrition of infants has been the apparent decalcifying effect of cereals. Largely because of the work of Mellanby,¹⁶⁹ it has been assumed that cereals contain a substance ("toxamin") which is responsible for the inhibiting effect of cereals on the calcification of bone. While it has been realized that this undesirable effect of cereals can be counteracted with vitamin D, it has seemed advisable to investigate the evidence in regard to the theory of a "toxamin," since cereals make up such a large part of the diet. The Council on Foods¹⁷⁰ has recently reported the results of such an investigation, and the conclusion reached is that there is no good evidence for the existence of a decalcifying factor in cereals and that the hypothesis of the existence of such a factor is not needed to explain experimental results. The concentration of calcium and phosphorus in the diet is just as important as is the ratio of the two substances in determining the occurrence and degree of rickets, and the concentration of phosphorus is determined partly by the amount of available phosphorus in the diet. Cereals contain phosphates in the form of phytin, in which state it is poorly utilized, consequently, if the diet contains a large amount of cereal there is likelihood of an insufficient absorption of phosphate, and rickets is more likely to occur. The Council concluded, therefore, that there "appears

168 Steck, I. E., Deutsch, H., Reed, C. I., and Struck, H. C. Further Studies on Intoxication with Vitamin D, *Ann Int Med* **10** 951-964 (Jan.) 1937.

169 Mellanby, Edward. Experimental Rickets, Medical Research Council, Special Report Series, no. 61, London, His Majesty's Stationery Office, 1921.

170 The Alleged Decalcifying Effect of Cereals, report of Council on Foods, *J. A. M. A.* **109** 30-31 (July 3) 1937.

to be no necessity at the present time to irradiate cereals or to add vitamin D substances to cereal products intended for general human consumption in order to overcome the harmful effects of a hypothetical toxin”

Ultraviolet Radiation—The effects of ultraviolet therapy are widespread, and while much information is lacking in regard to all the specific effects, it is clearly recognized that the value of ultraviolet therapy in rickets is due to the production of vitamin D in the skin. Coblentz¹⁷¹ and Luce-Clausen¹⁷² have recently reviewed, respectively, the physical and the chemical aspects of ultraviolet therapy. Luce-Clausen has pointed out that ultraviolet radiation is not a strong therapeutic agent in promoting the healing of fractures, nor do exposures sufficient to produce mild erythema and subsequent pigmentation result in beneficial effects in cases of pulmonary tuberculosis.

Toxicity of Cod Liver Oil—For several years there has been discussion of the possible toxic effect of cod liver oil. Burock and Zimmerman¹⁷³ have recently reinvestigated this problem. Using as experimental animals rats and mice, which are supposed to be particularly susceptible to cod liver oil, these workers reached the conclusion that, in view of the small percentage of animals with changes in the tissues, even after the consumption of large doses of cod liver oil, the claim that cod liver oil in therapeutic doses can exert injurious effects cannot be substantiated. Another point of interest which they noted is that Davson¹⁷⁴ has shown that the favorable results observed after the use of cod liver oil in wounds are due not to its vitamin D content but to the action of the oil in stimulating production of granulation tissue.

VITAMIN E

At least three substances possess the effect of vitamin E, and as yet it has not been clearly demonstrated that any one of them is required by man for normal health or reproduction. In fact, the necessity of vitamin E for normal embryonic growth in animals other than the rat and the mouse has not been established. Mattill,¹⁷⁵ in a recent review of the subject, pointed out that vitamin E is associated with antioxidants in nature and that it is readily susceptible to oxidative destruction. More specifically, it seems to play some essential role in

171 Coblentz, W. W. The Physical Aspects of Ultraviolet Therapy, J. A. M. A., to be published.

172 Luce-Clausen, Ethel M. Clinical Aspects of Ultraviolet Therapy, J. A. M. A., to be published.

173 Burock, Ethel, and Zimmerman, H. M. Studies on the Alleged Toxic Action of Cod Liver Oil, J. Nutrition **14** 535-551 (Dec.) 1937.

174 Davson, cited by Burock and Zimmerman¹⁷³.

175 Mattill, H. A. Vitamin E, J. A. M. A., to be published.

the nuclear activities involving chromatin and is indispensable, especially in tissues in which cellular proliferation and differentiation are unusually rapid

Of principal clinical interest is the possible etiologic role of a deficiency of vitamin E in threatened and spontaneous abortion and of an excess of the vitamin in malignant disease. Widespread interest has been aroused by the striking report of Rowntree, Lansbury and Steinberg¹⁷⁶ that when rats are fed a crude preparation of ether-extracted wheat germ oil, in addition to an ordinary stock ration, malignant tumors develop which have the character of spindle cell sarcoma and which involve the gastro-intestinal tract and peritoneal cavity. Mattill¹⁷⁵ said that whatever the agent causing these tumors may be, it is not vitamin E.

It is difficult to obtain proof that vitamin E is of value in the treatment of sterility and habitual abortion in human beings. While Shute¹⁷⁷ and others have continued to report satisfactory results with wheat germ oil in the treatment of such conditions as abruptio placentae, it seems reasonable to conclude with Mattill¹⁷⁵ that more clinical evidence is greatly needed to establish the usefulness of vitamin E therapy in abnormal human reproduction.

VITAMIN F

Interest in certain unsaturated fatty acids, such as linoleic acid, at one time known as vitamin F, has been aroused recently because in the advertisements of some cosmetologists it has been suggested that vitamin F is of value in the treatment of many abnormalities of the skin when added to the diet or when applied externally to the skin. Bacharach,¹⁷⁸ who recently reviewed the literature on the subject, found that there is a lack of any well established facts to justify the recommendation of vitamin F to the public for external application to the skin in cosmetics. Somewhat the same stand is taken by the Bureau of Investigation of the American Medical Association,¹⁷⁹ which has reported its investigation of a preparation of this type. However, Weinstein and Glennon¹⁸⁰ stated that these substances may be of value in a number of diseases of the skin, including allergic eczema.

176 Rowntree, L. G., Lansbury, John, and Steinberg, A. Neoplasms in Albino Rats Resulting from the Feeding of Crude Wheat Germ Oil Made by Ether Extraction, *Proc Soc Exper Biol & Med* **36** 424-426 (April) 1937

177 Shute, Evan. The Early Diagnosis of Abruptio Placentae and Its Treatment with Wheat Germ Oil, *Am J Obst & Gynec* **33** 429-436 (March) 1937

178 Bacharach, A. L. Vitamin F, *Nutrition Abstr & Rev* **7** 355 (Oct) 1937

179 Rats and Vitamin F (?) in Cosmetology, report of Bureau of Investigation, *J A M A* **108** 1279 (April 10) 1937

180 Weinstein, M. L., and Glennon, Katharyn. Vitamin F Ointments, *Illinois M J* **71** 477-479 (June) 1937

VITAMIN K

Little of clinical significance concerning the usefulness of the antihemorrhagic factor known as vitamin K has been added to that noted in the review last year. Apparently this substance may play some role in the production of prothrombin, for in certain species of animals, deficiency of vitamin K leads to a decrease in the prothrombin content of the blood. The possible importance of this observation in cases of jaundice in which bleeding may be a serious symptom has recently been discussed editorially in *The Journal of the American Medical Association*¹⁸¹ and is illustrated by the fact that the prothrombin content of the blood of patients with jaundice has been found to be diminished. Since vitamin K is fat soluble and there is frequently interference with the absorption of fat in patients with obstructive jaundice, the possibility has been suggested that the prothrombin deficiency of jaundiced patients may be due to deficiency of vitamin K. So far, studies on this phase of the problem have not been reported, although therapeutic trial is clearly indicated. In fact, with the exception of the report of Dam, Schönheyder and Lewis,¹⁸² who observed no beneficial effect from the use of vitamin K in a case of hemophilia, little is known of the possible influence of the substance in man.

Almquist,¹⁸³ who has been actively engaged in studying vitamin K metabolism in chickens, has obtained the antihemorrhagic substance in the form of a colorless crystalline fraction extracted from commercially dehydrated alfalfa. It contains one or two benzene rings. Almquist and Stokstad¹⁸⁴ have also described a rapid procedure for the assay of vitamin K in chicks.

VITAMIN T

A description of possibly another new dietary factor which may be of importance in influencing the blood has been given by Schiff and Hirschberger,¹⁸⁵ who found that it is possible to produce with regularity an increase in the number of platelets in the blood of normal children. The unknown factor responsible for this reaction is present in sesame

181 Prothrombin Deficiency in Jaundiced Patients, editorial, *J A M A* **108** 2043-2044 (June 12) 1937

182 Dam, Henrik, Schönheyder, Fritz, and Lewis, Liese. The Requirements for Vitamin K of Some Different Species of Animals, *Biochem J* **31** 22-27 (Jan) 1937

183 Almquist, H J. Further Studies on the Antihemorrhagic Vitamin, *J Biol Chem* **120**.635-640 (Sept) 1937

184 Almquist, H J, and Stokstad, E L R. Assay Procedures for Vitamin K (Antihemorrhagic Vitamin), *J Nutrition* **14** 235-240 (Sept) 1937

185 Schiff, E, and Hirschberger, C. Thrombocytosis Produced by a Hitherto Unknown Substance—the "Fat-Soluble T Factor," *Am J Dis Child* **53** 32-38 (Jan) 1937

oil but not in cod liver oil or olive oil and is therefore not vitamin A. From 8 to 10 drops a day of sesame oil was an effective dose in producing a rise in the platelet count. Schiff and Hirschberger have suggested that this may be a new fat-soluble vitamin, for the present designated as the fat-soluble T factor.

VITAMIN P

Szent-Gyorgyi,¹⁸⁶ who has played such a prominent part in the isolation and studies of the chemical activity of vitamin C, recently announced that deficiency of vitamin C is not the only factor responsible for experimental scurvy. He stated as his opinion that another substance, which he named vitamin P, although not responsible alone for any clinical symptoms, when present in deficient amounts greatly modifies the pathologic picture of vitamin C deficiency in the experimental animal. Vitamin P appears to be closely related to vitamin C and is a natural companion of vitamin C in plants. Zilva¹⁸⁷ and his associates were unable to confirm these findings.

ANTI-GIZZARD-EROSION FACTOR

In one of his early papers on hemorrhagic disease in chicks, Dam¹⁸⁸ reported among other abnormalities associated with this disease the occurrence of erosion in the gizzard. Recently, because of the great interest in the possible relation of ulcerating lesions of the stomach and duodenum to deficiency syndromes, attention has been focused again on this observation, which has been repeatedly confirmed. It has been shown clearly that the responsible factor is not identical with vitamin K, since the former is thermolabile and is contained in the saponifiable fraction of alfalfa, whereas vitamin K is heat resistant and occurs in the unsaponifiable fraction of alfalfa. The anti-gizzard-erosion factor is found in alfalfa as well as in kale, hempseed, wheat bran and other greens and cereals. Ivy¹⁸⁹ suggested that the primary defect resulting from the deficiency of the anti-gizzard-erosion factor may be resident in the liver rather than in the gastric mucosa. Cheney¹⁹⁰ has reported that the factor is curative as well as preventive of erosion.

186 Bentsath, A., Rusznyak, S., and Szent-Gyorgyi, A. Vitamin P, *Nature*, London **139** 326-327 (Feb. 20) 1937.

187 Zilva, S. S. Vitamin P, *Biochem. J.* **31** 915-919 (June) 1937.

188 Dam, Henrick. Cholesterinstoffwechsel in Huhnereiern und Huhnchen, *Biochem. Ztschr.* **215** 475-492, 1929.

189 Ivy, A. C. The Anti-Gizzard-Erosion Factor, *Am. J. Digest. Dis. & Nutrition* **4** 121 (April) 1937.

190 Cheney, Garnett. Gastro-Enterology in 1936. Selected Topics, *Arch. Int. Med.* **60** 703-729 (Oct.) 1937.

in the gastric mucosa and that restoration to a normal-appearing mucosa takes place within about three weeks after adequate amounts of alfalfa have been added to the previously deficient diet of chicks with mucosal erosions. As yet there is no evidence to indicate that the anti-gizzard-erosion factor is of importance in man. It seems doubtful that it will prove of much importance in the problem of peptic ulcer, but much clinical observation will be needed to settle this point.

PROTEIN

Interesting work on the biologic aspects and nutritive significance of proteins has been reported by Beigmann and Niemann¹⁹¹ and by Rose¹⁹². As a result of extensive studies of amino-acids Rose noted that there are twenty-two common amino-acids, of these, ten are essential, namely, lysine, tryptophan, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine.

The old problem of the protein requirement of man has been reviewed again by Leitch and Duckworth¹⁹³. They have estimated that the requirement for adults on a mixed diet, including animal and plant protein, is about 50 Gm daily. Evidence is presented which indicates that an intake considerably above this level may be required for the maintenance of health and for a high state of physical development. No evidence has been presented to show that a high protein diet is harmful. Because of these conclusions, which are in fundamental agreement with those of most experts on nutrition, it is of interest to read the report by Strieck¹⁹⁴ of metabolic studies of a healthy man of 70 years who for years had been on a diet containing about 30 Gm of protein daily. The physical efficiency of this man was excellent, and he maintained a positive nitrogen balance except when sick. In fact, there was no increased excretion of nitrogen after the most strenuous bodily labor. Akyroyd¹⁹⁵ reported that deficiency disease and malnutrition are extremely common in the South of India, and that the children of one group of inhabitants live on tapioca only. The average dietary intake amounts to approximately 2 pounds (900 Gm) of tapioca a day, which has a

191 Beigmann, Max, and Niemann, Carl. New Biological Aspects of Protein Chemistry, *Science* **86** 187-190 (Aug 27) 1937.

192 Rose, W. C. The Nutritive Significance of the Amino Acids and Certain Related Compounds, *Science* **86** 298-300 (Oct 1) 1937.

193 Leitch, I., and Duckworth, J. D. The Determination of the Protein Requirements of Man, *Nutrition Abstr. & Rev.* **7** 257-267 (Oct) 1937.

194 Strieck, F. Metabolic Studies in a Man Who Lived for Years on a Minimum Protein Diet, *Ann. Int. Med.* **11** 643-650 (Oct) 1937.

195 Akyroyd, W. R. The Assessment of the "State of Nutrition" and the Detection of Malnutrition, *Brit. M. J.* **2** 1008-1010 (Nov 20) 1937.

caloric value of 1,500 and contains about 12 Gm of protein. With this low intake of protein, the children survive, although they are poorly nourished.

IRON

Each year brings a little clearer understanding of the nutritional value of iron and of the relation of deficiencies of iron to anemia. As Heath and Patek¹⁹⁶ have noted in their extensive review of the anemia of iron deficiency, the extent of the deficiency in this disease can be determined quantitatively at any time from the hemoglobin content of the blood, and the deficient factor, iron, can be supplied quantitatively. They have stated that while 12 to 15 mg of iron daily is usually considered to be an optimal intake, diets containing much less than this amount will maintain the iron balance. Increased demands for iron are noted during growth, pregnancy, lactation and menstruation. The authors expressed the belief that need for iron and loss of iron must play a primary role in the causation of hypochromic anemia, whereas dietary deficiency of iron or malabsorption of iron in a diseased gastrointestinal tract is of secondary importance.

Some other interesting observations and speculations regarding the effectiveness of massive doses of iron in hypochromic anemia have been advanced by Fowler and Barer¹⁹⁷ and by Brock and Hunter¹⁹⁸. These observers noted that when large amounts of iron were administered, much more iron was absorbed than was converted into hemoglobin. For example, in Fowler and Barer's study an average of 32.6 per cent of the iron administered orally in the form of iron and ammonium citrates was retained, but only approximately 1.96 per cent of the iron administered was utilized in the formation of hemoglobin. In fact, as Brock¹⁹⁹ demonstrated, if smaller than massive doses of iron are administered or if treatment is interrupted prematurely, many patients will not be cured, despite the absorption and deposition of large quantities of the metal.

Following through with this evidence and that produced by their studies of iron metabolism in polycythemia vera, McCance and Widdowson²⁰⁰ have propounded an interesting new theory of the absorption

196 Heath, C. W., and Patek, A. J., Jr. The Anemias of Iron Deficiency, *Medicine* **16** 267-350 (Sept.) 1937.

197 Fowler, W. M. and Barer, A. P. Retention and Utilization of Orally Administered Iron, *Arch. Int. Med.* **59** 561-571 (April) 1937.

198 Brock, J. F., and Hunter, Donald. The Fate of Large Doses of Iron Administered by Mouth, *Quart. J. Med.* **6** 5-16 (Jan.) 1937.

199 Brock, J. F. Relation Between Hypochromic Anemias and Iron Deficiency, *Brit. M. J.* **1** 314-320 (Feb. 13) 1937.

200 McCance, R. A., and Widdowson, E. M. The Fate of the Elements Removed from the Blood-Stream During the Treatment of Polycythemia by Acetyl-Phenyl-Hydrazine, *Quart. J. Med.* **6** 277-286 (July) 1937, Absorption and Excretion of Iron, *Lancet* **2** 680-684 (Sept. 18) 1937.

and excretion of iron. They have concluded that the body has little power of excreting iron and that the metabolism of iron under normal circumstances is governed by the control of iron absorption rather than by the excretion of iron. The concentration of iron in the plasma is normally low and when it rises, the excess is stored. The concentration of iron in the intestine of a person on a normal diet is usually so low that the diffusion gradient is not steep enough for much absorption to occur unless the concentration in the body fluids and tissues is subnormal as in anemia following hemorrhage. When iron is administered in massive doses the diffusion gradient in the intestine rises and a positive balance is established. It is believed that the bone marrow is sluggish in hypochromic anemia and that it is stimulated only by the presence of a high concentration of iron which it is difficult for the plasma to maintain because of the storage capacities of certain organs. The threshold phenomenon is consequently one of a threshold of marrow stimulation rather than of intestinal absorption. Barer and Fowler²⁰¹ have indicated that patients with achlorhydria show a decreased retention of iron with an ordinary dietary intake of iron but that achlorhydria does not influence the retention of iron when large amounts are given by mouth. The addition of hydrochloric acid did not increase the retention of iron with either a high or a normal intake of iron.

Another interesting problem in iron metabolism which seems a little closer to solution concerns the mechanism which prevents more than the expected degree of anemia in infants after birth and during the period when milk is the principal if not the only source of nourishment and the intake of iron is not equal to the demands. Previously it has been suspected that the store of iron in the liver serves as the reservoir to "carry over" the blood during this period but recently it²⁰² has been observed that the hepatic reserve is not so large as was previously thought to be the case and that the demand for iron is satisfied by conservation of that which is present in erythrocytes destroyed during the early months of life.

COBALT

That cobalt may be one of the "little things" in nutrition is suggested by the observations of Denham²⁰³ that domestic animals in New Zealand which have "bush sickness" may be treated with amazing suc-

201 Barer, A. P., and Fowler, W. M. Influence of Gastric Acidity and Degree of Anemia on Iron Retention. *Arch. Int. Med.* **59**:785-792 (May) 1937.

202 Iron Metabolism in Early Infancy, editorial. *J. A. M. A.* **109**:279 (July 24) 1937.

203 Denham, H. G. Cobalt Investigation in New Zealand. *Science* **85**:383 (April 16) 1937.

cess by the addition of traces of cobalt to the diet Kato²⁰⁴ said that cobalt when administered in doses of approximately one tenth that of iron appeared to accelerate the formation of erythrocytes and hemoglobin in the blood of infants with nutritional anemia

ZINC

Hove, Elvehjem and Hart²⁰⁵ studied zinc deficiency in rats and were able to prevent it by giving 40 micrograms of zinc daily They postulated that zinc is involved in the production or utilization of some hormone of the pituitary gland which controls the motility and tonus of the intestinal tract

POTASSIUM AND MAGNESIUM

Since Addison's disease is being successfully treated by several measures, one of the most useful of which is a diet low in potassium, it is of interest to note the report of Schriader, Prickett and Salmon²⁰⁶ on the effects of potassium and magnesium deficiency in the rat Characteristic symptomatic and pathologic changes developed in these animals and resulted in death in an average of three to five weeks The deficiency of potassium and magnesium in these animals was marked, while in patients with Addison's disease the intake of potassium is usually reduced to 2 Gm daily Wilder²⁰⁷ has reported that at the Mayo Clinic no untoward effects have been observed in patients with Addison's disease treated with a low potassium diet

CALCIUM

There have been two reports of interest during the past year in regard to the calcium requirements of man and the value of calcium therapy in dentistry

Leitch,²⁰⁸ of the Imperial Bureau of Animal Nutrition of the Rowett Research Institute, in Aberdeen, has summarized the available evidence on the calcium requirements of man He found that the maintenance requirement of calcium for adults is estimated as 0.55 Gm daily (Sherman estimated it as 0.45 Gm) There is no evidence to show

204 Kato, K Iron-Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, *J Pediat* **11** 385-396 (Sept) 1937

205 Hove, E, Elvehjem, C A, and Hart, E B The Physiology of Zinc in the Nutrition of the Rat, *Am J Physiol* **119** 768-775 (Aug) 1937

206 Schrader, G A, Prickett, C O, and Salmon, W D Symptomatology and Pathology of Potassium and Magnesium Deficiencies in Rats, *J Nutrition* **14** 85-104 (July) 1937

207 Wilder, R M Personal communication to the author

208 Leitch, I The Determination of Calcium Requirements of Man, *Nutrition Abstr & Rev* **6** 553-578 (Jan) 1937

what additional allowance is required "for health," but it is probable that such an allowance should be made. Leitch said the evidence suggests that senile osteoporosis may be due in part, at least, to calcium deficiency and that the daily minimum gross requirements, assuming a maximal probable retention of 50 per cent of the intake, is as follows

Age	Gm
6 months to 2 years	0.8
2 to 9 years	0.9
9 to 15 years	1.0
15 to 16 years	2.0
16 to adult age	Gradual decrease to adult level

In another summary of the present situation in regard to calcium therapy in dentistry the Council on Dental Therapeutics of the American Dental Association²⁰⁹ made the following report

1 All the calcium and phosphorus requirement for average needs, including pregnancy and growth, may be suitably obtained by means of an adequate diet containing not only calcium and phosphorus but also other necessary factors, such as caloric, protein and other mineral and vitamin requirements. 2 There is no carefully controlled evidence that the addition of calcium and phosphorus compounds, whether inorganic or organic, promotes retention of these elements and hence freedom from dental disorders except in known cases of deficiency. 3 There is no evidence that the injection of combinations of calcium and phosphorus in addition to diets adequate in these elements promotes the development of sound teeth in the human fetus. The calcification of teeth is a postnatal event.

THE SIGNIFICANCE OF MILD FORMS OF DEFICIENCY DISEASES

Modern clinicians, public health experts, hygienists, experts in dietetics and others interested in public health may well feel confused about the real significance of much of the information that is so rapidly accumulating in the field of nutrition. How is one to meet the major problems of nutrition which Minot said "concern supplying a diet optimal in multiple factors for each given individual at each stage of life"? We are also reminded that "nutrition intimately concerns the welfare of man and his place in future history will depend in no small part on what he decides to eat." One almost wonders how man was successful in keeping alive and healthy during the thousands of years preceding the past twenty-five years, which have seen the dawn of the "newer knowledge of nutrition." Perhaps one explanation may be the wide limits which exist in the capacity of the animal organism to meet its environment. However, an interesting editorial entitled "Brown

²⁰⁹ Council on Dental Therapeutics of the American Dental Association, cited in Calcium Therapy in Dentistry, editorial, J. A. M. A. **108** 1655-1656 (May 8) 1937.

Bread Versus White," which has been published in a recent number of the *British Medical Journal*,²¹⁰ offers another explanation. By means of careful estimations of the vitamin B₁ content of brown bread and of white bread and of the rations of bread consumed by soldiers and by citizens of Great Britain many years ago as compared with those consumed today, it was found that the change in character and consumption of bread alone has caused a reduction in available vitamin B₁ from 550 to less than 60 international units a day (500 international units probably represents the physiologic requirement). It was estimated that the ration of the soldier in 1670 contained 1,000 international units of vitamin B₁ a day and that in 1782 the diet of the parish poor contained 660 to 850 units. Indeed, the best-fed members of the population today, while receiving twice as much vitamin B₁ as is received by persons with a low income, consume less vitamin B₁ than did the parish poor of the eighteenth and early nineteenth centuries.

Publication of several reports of nutritional surveys of various groups of the population of this country and of England suggests that malnutrition and deficiency diseases are common. On the other hand, it is difficult to convince skeptics who are not of this belief, because criteria are still indefinite and a standard of the state of nutrition is difficult to define. Some progress is being made in this direction, however. During the World War and in the postwar period, such simple physical characteristics as weight, height and age were taken to indicate the nutritional status of the individual. As knowledge of the vitamins advanced, previous criteria of nutritional standards have been modified to include the presence or absence of gross evidence of deficiency disease, and as information has accumulated leading to interest in the physiologic changes which occur before gross pathologic changes become manifest in deficiency disease, the problem of the assessment of nutrition has become increasingly more difficult.

Reports of methods of assessing the nutritional status of individuals have been published by McCollum²¹¹ and by the Health Organization of the League of Nations.²¹² Methods of assessing the incidence of certain phases of deficiency disease have been reported by many workers, as noted previously in this review. Some of these indicate that apparently minor physiologic alterations, such as slight impairment of the ability to adapt the eyes to darkness or a content of vitamin C in

210 Brown Bread Versus White, editorial, *Brit M J* 2 752-753 (Oct 16) 1937

211 McCollum, E. V. Nutrition and Public Health, *Proc Ann Conf, Milbank Memorial Fund*, April 1937, pp 61-75

212 Report on the Work of the Group of Experts Appointed to Study Methods of Assessing the State of Nutrition in Infants and Adolescents, *Bull Health Organ, League of Nations* 6 129-204 (April) 1937

the blood and urine below so-called normal levels, are common even among such well fed persons as Americans. Those who present these physiologic changes are usually unaware of them, and special tests are required for their detection. These changes can usually be corrected by administration of the vitamin which is deficient, but, again, the subject may notice no effect after such treatment.

What is the significance of these findings? Does it matter if otherwise normal persons have such slight physiologic alterations? As the *Lancet* stated editorially,²¹³ "the physiologist will be quite sure that it does." The answer is that no one knows, but that such changes are probably significant seems reasonable to believe, for, as Minot²¹⁴ has well expressed it:

If the optimal, not usual, diet for man at all ages and under varying circumstances of his activity and environment were known, and if throughout generations each person took an ideal diet—one nicely adjusted with respect to all its constituents at an optimal level for the best possible achievement—not only would much illness be prevented but the physical and mental development of man would be improved, leading to consequences of vast importance.

Latent Deficiency Disease—In previous sections of this review it was pointed out that it has been possible by selection and inbreeding to develop two strains of rats that in appearance were alike save that one of them reacted more severely to a rachitic diet than the other. This is a rather startling example of the effects of inbreeding and selection and illustrates the fact that some of the characteristics which make up individual variations are the result of fundamental and inheritable reactions of living things. In this connection, recent studies reported by Bloomfield²¹⁵ and by French and Bloomfield²¹⁶ are of considerable interest. Bloomfield observed that when a series of rats of the same breed and of approximately the same age were placed on a defective diet, there was great individual variation in the loss of weight. Since on repetition of the experiment after the loss of weight had been restored by a normal diet, the rats which lost the most weight in the first instance tended to do so again, it is suggested that resistance to loss of weight with a defective diet seems to be in some cases a characteristic of the individual and not a matter of chance. From observations of a somewhat similar character, French and Bloomfield reported that rats which had lost weight as a result of a defective diet

²¹³ An Objective Test of Nutrition? editorial, *Lancet* **2** 1025 (Oct. 30) 1937.

²¹⁴ Minot, G. R. *Harvard and Nutrition*, *New England J. Med.* **215** 1147-1149 (Dec. 17) 1936.

²¹⁵ Bloomfield, A. L. Individual Variations in Susceptibility to Dietary Deficiency, *J. Nutrition* **14** 111-116 (Aug.) 1937.

²¹⁶ French, L. R., and Bloomfield, A. L. "Latent Deficiency" in Rats. Variations in Weight Loss on Repeated Feeding of a Defective Diet, *J. Nutrition* **14** 117-129 (Aug.) 1937.

and had then been restored to "normal" by stock rations showed a more rapid loss of weight if placed on the same deficient diet for a second time. It is remarkable to note that this unexplained phenomenon of "secondary rapid weight loss" will occur after as long an interval as eighty days between the first and the second period of defective dietary intake. These findings present experimental evidence in keeping with clinical observations that the undesirable influence of a faulty diet in the zone of partial deficiency may become detectable only after years or generations and that a deficient diet may impair considerably the vigor and resistance of the individual for some period after resumption of a normal diet.

Sprue—In the review published last year, note was made of the remarkable effect of liver extract on the appearance of the gastric mucosa of patients with pernicious anemia and on the motor functional activity of the small intestine of patients with sprue without anemia. Barker and Rhoads²¹⁷ have extended the latter studies to include the effect of liver extract on the absorption of fat in sprue. They stated that they were inclined to feel that in sprue, liver extract exerts some specific effect on the absorptive power of the intestinal tract, because in 3 of 5 cases of sprue, previous inability to absorb fat in normal quantities was overcome, and the postabsorptive levels of fat in the blood approached the normal.

MISCELLANEOUS OBSERVATIONS

Reports of the Council on Foods of the American Medical Association—During the past year the Council on Foods of the American Medical Association has issued a series of reports which summarize in a judicial way information of considerable interest in regard to certain phases of nutrition. These include reports entitled "The Nutritional Significance of the Curd Tension of Milk,"²¹⁸ "The Nutritional Value of Spinach,"²¹⁹ "The Alleged Decalcifying Effect of Cereals,"¹⁷⁰ and "Strained Fruits and Vegetables in the Feeding of Infants."²²⁰ In summarizing the evidence on the significance of the curd tension of milk, the Council made the following statement:

In general, milk that has a low curd tension as determined by appropriate laboratory methods leaves the stomach more quickly than milk that does not

217 Barker, W. H., and Rhoads, C. P. The Effect of Liver Extract on the Absorption of Fat in Sprue, *Am. J. M. Sc.* **194**: 804-810 (Dec.) 1937.

218 The Nutritional Significance of the Curd Tension of Milk, report of the Council on Foods, *J. A. M. A.* **108**: 2040-2041 (June 12), 2122-2123 (June 19) 1937.

219 The Nutritional Value of Spinach, report of Council on Foods, *J. A. M. A.* **109**: 1907-1909 (Dec. 4) 1937.

220 Strained Fruits and Vegetables in the Feeding of Infants, report of Council on Foods, *J. A. M. A.* **108**: 1259-1261 (April 10) 1937.

have this property The evidence is meager, however, that any soft curd milks are "better digested" or more completely digested than ordinary boiled milk

The gist of the report on the alleged decalcifying effect of cereals has been noted in the section on vitamin D. In summarizing the evidence on spinach the Council noted that

Spinach may be regarded as a rich source of vitamin A and as a contributor of vitamin C, iron and roughage to the diet. While the total iron content of spinach is high as compared with other vegetable foods, the evidence shows that this iron is not wholly available and is not well utilized by infants. Evidence regarding the amount of the iron of spinach that is available to older children and adults has not been reported at the present time. The calcium of spinach is not well utilized by the organisms because it is present largely in the form of calcium oxalate, which is insoluble in the fluids of the alimentary tract.

Summaries or Symposia of Importance in Nutrition—During the past year there has appeared a book entitled "The Avitaminosis" by Eddy and Dalldorf²²¹ which covers most of the chemical, clinical and pathologic aspects of the vitamin deficiency diseases. For those who may be interested in some of the recent advances in nutritional research, particularly with regard to the chemistry of vitamins, reference may be made to an article by McCollum²²². Another excellent summary of nutrition and of deficiency diseases is that published by a group of workers on problems of nutrition at Harvard, having been presented by them at the Harvard Tercentenary Celebration²²³. A practical handbook, which is a brief compendium of new information about the chemistry of the vitamins, units of measurement and tables of the vitamin content of foods, has just been issued by the United States Department of Agriculture. This excellent summary, which will be invaluable to dietitians, is entitled "Vitamin Content of Foods". It was compiled by Esther P. Daniel and Hazel E. Munsell²²⁴ and may be obtained from the Government Printing Office for 15 cents.

221 Eddy, W. H., and Dalldorf, Gilbert. *Avitaminosis*, Baltimore, Williams & Wilkins Company, 1937.

222 McCollum, E. V. *Recent Advances in Nutritional Research*, J. Michigan M. Soc. **36** 211-227 (April) 1937.

223 Minot, G. R., and others. *Symposium on Nutrition and the Deficiency Diseases*, New England J. Med. **215** 1147-1166 (Dec. 17) 1936.

224 Daniel, Esther P., and Munsell, Hazel E. *Vitamin Content of Foods*, Miscellaneous Publication 275, United States Department of Agriculture, June 1937.

News and Comment

AMERICAN PHYSICIANS' ART ASSOCIATION EXHIBITION

The American Physicians' Art Association, a national organization of members of the medical profession who have ability in the fine arts, will hold its first national exhibition in the San Francisco Museum of Art in June 1938 (The Annual Session of the American Medical Association will be held from June 13 to 17 in the same city)

The American Physicians' Art Association already has an outstanding membership. There are three classifications for membership: active, associate and contributing.

The first annual exhibition of the association promises to be of unusual interest, with entries to be accepted (after selection by a jury) in the following classes: oils, watercolors, sculpturing, photographs, pastels, etchings, crayon drawings, pen and ink drawings (including cartoons), wood carvings and book bindings. Scientific medical art work will not be accepted. The exhibition is not limited to first showings. All entries must be received by April 1. Any physician interested should communicate at once with the Secretary of the American Physicians' Art Association, Suite 521-536 Flood Building, San Francisco.

Book Reviews

Functionelle Pathologie By Gustav von Bergmann Second edition Price, 25 marks Pp 547, with 73 illustrations Berlin Julius Springer, 1936

The new edition of this text will be welcomed with the same enthusiasm which attended the presentation of the first edition in 1932 Von Bergmann approaches disease from the standpoint of functional pathology, proceeding from a general discussion in the first chapter to a specific consideration in succeeding chapters of the important organs—colon, stomach, pancreas, duodenum and biliary tract, followed by a consideration of inflammation, the vitamins and hormones, diabetes, thyroid states and vascular, cardiac and nervous problems Such an approach to disease is stimulating in at least two ways First, it integrates for the reader related diseases and passes from the normal to the abnormal function of organs with a clarity of understanding impossible to attain from a study of the isolated disease entities alone Second, it instills in the student of disease a realization of the importance of knowledge of normal function of tissues, leading to an easy comprehension of the mechanisms of disease

When possible the author leads to new concepts through a brief historical approach, and although his own researches and views are presented, full consideration is given controversial subjects, for example, the etiology of peptic ulcer The reader is not denied the opportunity to judge conflicting data Von Bergmann's investigative interests have been so wide in their scope that, whether the reader is a gastro-enterologist, cardiologist or psychiatrist, he will feel the unusual familiarity and knowledge of the author in his particular field Free reference is made to the important literature, which is, of course, chiefly continental, and a bibliography is appended to each chapter

The rarity of adequate texts of this type and the wide interests of the author, who is in active touch with so many branches of the fields covered, will make this book of interest not only to the general reader but as well to those who specialize in the various subdivisions of internal medicine

Einführung in die pathologische Physiologie By Max Burger Second edition Price, 24 marks Pp 454, with 43 illustrations Berlin Julius Springer, 1936

Twelve years have elapsed since the first edition of this text appeared The remarkable advances in knowledge of the mechanisms of disease since that time have demanded a complete rewriting, particularly of the important chapters on the vitamins, nutrition and the endocrine glands The elapse of such a long time makes one wonder why the author has failed to keep this work abreast in a field continually bristling with activity and new thought

The well known aspects of deranged bodily function are treated under the usual headings, such as respiration, nervous system, metabolism, endocrine glands, blood and heart Much of the work is sketchily done and at times, particularly in more recent advances originating outside Germany, the newer knowledge is either omitted or only briefly mentioned This is well shown in the discussion of the pathologic physiology of the parathyroid glands, the relationship of the pituitary glands to carbohydrate metabolism and the mechanisms of the anemias The work of Houssay is not given its place Castle's observations leading to the present concepts of the mechanism of macrocytic anemia are considered chiefly outside the section on blood Apparently the compilation of data on insulin was made too early to include those on protamine insulin

Briefly, one notes the omission of many data that should rightfully be included in a text of this size and scope

Synopsis of Diseases of the Heart and Arteries By George R Herrmann, M D, Ph D, Professor of Clinical Medicine, the University of Texas Price, \$4 Pp 344, with 91 illustrations St Louis C V Mosby Company, 1936

The author presents this book to fill what he considers a need for a synopsis of diseases of the heart and arteries In the opinion of the reviewer it is more than a synopsis, running to the length of some textbooks on the subject

There are a number of inaccuracies in the book, and too many dogmatic statements are made without qualification This is probably because of the author's original intention of writing the book as a synopsis For example, on page 277 the statement that aortic stenosis is the rarest of (cardiac) lesions is inaccurate In addition, many points of practical importance have been omitted There is also a tendency to give the impression that certain work has been proved to be of value which as yet is not generally accepted Some chapters, such as those on congenital heart disease, diseases of the great vessels and peripheral vascular diseases, are discussed so briefly as to be of little value Other chapters, such as the chapter on studies of patients suspected of having heart disease and subsequent chapters in which the various types of heart disease are presented according to etiology, could have been greatly condensed

The book is therefore too long for a synopsis, it overemphasizes certain subjects and it does not give sufficient space to other important subjects It offers nothing original or particularly new and probably will be disappointing to those for whom it was intended "the plodding student and the assiduous conscientious practitioner"

Medical Urology By Irvin S Koll, M D, Attending Urologist, Michael Reese Hospital, Chicago Price, \$5 Pp 431, with 92 illustrations and 6 colored plates St Louis C V Mosby Company, 1937

The author says that his principal idea in writing this work was to present the subject of urology so as to be of practical value to the general physician and an aid to the medical student As a general physician, this reviewer wishes to congratulate the author

The entire volume is so clearly and sanely written that many of the intricacies of the anatomy, physiology and pathology of the genito-urinary organs become readily understandable, as do many of the problems which face the modern urologist Moreover, since the purpose of the book is to discuss urology for the general reader rather than for the specialist, no space is wasted on too elaborate descriptions of operative technic On the other hand, appropriately lengthy discussion is given to the less complicated prophylactic, diagnostic and therapeutic procedures in the field, with which every physician should be familiar

The book is well printed and excellently illustrated It is of convenient size and shape It is thoroughly readable On the whole, it gives every promise of becoming one of those happy texts necessarily fated to have a long and useful existence

Argentine Archives of the Diseases of the Respiratory System and Tuberculosis, Buenos Aires, Vol 4, no 1-4, 1936

This journal is devoted to the pathology of the respiratory tract and tuberculosis Each number constitutes a volume of from 100 to 150 pages and is profusely illustrated, containing sections of original work, reports of conferences, proceedings of medical societies, abstracts, bibliographies and reviews of tuberculosis and antituberculosis information Volume 4 is devoted entirely to bronchography, with chapters by various authors on indications and various technics, and includes a description of the normal anatomy of the respiratory tract as visualized by means of opaque oils Other chapters discuss bronchography in asthma and chronic bronchitis, carcinoma, atelectasis, bronchiectasis, tuberculosis and tumors of the pleura The use of opaque oils in determining the etiology of hemoptysis also is discussed One of the most outstanding articles is that by Drs Egidio S Mazzei, Juan A Aguirre and Miguel E Jorg, in which they present the subject of the relation of the genesis of the alveoli to congenital bronchiectasis

The Harvey Lectures Delivered Under the Auspices of the Harvey Society of New York, 1935-1936 Series 31 Price, \$4 Pp 255 Baltimore Williams & Wilkins Company, 1936

As to be expected, this group of lectures is as instructive and interesting as those of the past. The present group of eight lectures covers an extensive variety of studies. "Proteins and Proteolytic Enzymes" by Max Bergmann, "The Significance of Chimpanzee-Culture for Biological Research" by Robert M. Yerkes, "The Virus Tumors and the Tumor Problem" by Peyton Rous, "Relations Between the Parathyroid, the Hypophysis and the Pancreas" by B. A. Houssay, "The Interrelation of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions" by John Farquhar Fulton, "The Influenzas of Swine and Man" by Richard E. Shope, "Malignant Cells" by Warren H. Lewis and "The Physiology of the Bronchial Vascular System" by I. de Burgh Daly. The respective subjects are summarized and interpreted by outstanding investigators in their particular fields. Time devoted to reading these lectures will be well spent.

Die Diät- und Insulinbehandlung der Zuckerkrankheit By Franz Depisch Price, 4.80 marks Pp 136 Vienna Julius Springer, 1937

This little volume has a definite place in medical literature. It does not supplant the larger, more distinguished monographs, references are not quoted, and details on controversial aspects of the disease find no place in its pages. Instead, the author gives the student and practitioner a concise introduction to the elements of the modern management of the diabetic patient in a straightforward and easily read style. A discussion of the use of terms and of variations in and regulation of the blood sugar content precedes a brief consideration of the mechanisms of carbohydrate metabolism. Diagnostic pitfalls and the principles of diagnosis are illustrated by case records. Treatment is divided into dietetic handling and management with insulin. Both are clearly developed, but the use of protamine insulin is not included. At the end of each section a number of maxims useful in practice are listed.

The book, to this reviewer, admirably fulfils its purpose.

Textbook of Medicine By Various Authors Edited by J. J. Conybeare Third edition Price, \$7 Pp 1,027, with 49 illustrations (24 roentgenograms) Baltimore William Wood & Company, 1936

The reviewer has reported on previous editions of this book and has always commented favorably. The section on neurology by Walshe seems to be by far the best to be found in any one volume work on practice. The whole text is well written. One may criticize perhaps the ultraconservative point of view adopted at times. Here and there it would have been better to concentrate on what is definitely established to be of value. In the section on renal function, for example, a number of tests which have been generally discarded are still described. In testing gastric secretion the writer always refers to histidine, whereas he probably means histamine. These are minor criticisms, however, and on the whole the book is to be recommended.

Clinical Allergy By Albert H. Rowe Price, \$8.50 Pp 812 Philadelphia Lea & Febiger, 1937

Rowe deals with the complex subject of allergy in a lucid, readable manner. With his extensive background of interest in the subject, what he has to say is reinforced by personal experience, which is so necessary in giving an adequate presentation to the reader. The general question of allergy is taken up first, and then come special sections on diseases and symptom complexes in which allergy does, or is supposed to, play a part. Every allergist in the reviewer's experience is an enthusiast, and the general physician may wonder whether or not a point is not strained sometimes in bringing forward an allergic explanation of this or that medical phenomenon. The same difficulty is felt when a monograph on endo-

crine disease, vitamin deficiency or any other specialized subject is read. If the general reader, however, preserves his own critical sense, he will find this book an admirable storehouse of information on allergy.

Manifestaciones pulmonares del cuy en el soroche agudo. Estudio anatómo-patológico y consideraciones patogénicas. By Pablo Mori Chavez, M.D. Pp 59, with 5 illustrations. Lima, Peru. Facultad de Ciencias Medicas de la Universidad Mayor de San Marcos, 1936.

When guinea-pigs were taken from sea level immediately to an altitude of 4,500 or 5,000 meters they showed dyspnea, and a large percentage of them died within from three to five days. At autopsy the lungs showed severe congestion. If death did not occur within the first week, acclimation usually resulted. This adjustment was manifested by the formation of large numbers of new minute blood vessels in the lung. The immediate reaction of guinea-pigs to high altitude indicated marked sensitivity to low oxygen tension, but the capacity for final adjustment was exceptionally good, which is in contrast to the severe pulmonary changes occurring in cats living for a few months at a high altitude. The report contains much of interest. Sixteen photomicrographs of pulmonary tissue are included.

Applied Dietetics. By Frances Stern. Price, \$3.50. Pp 263, with 52 tables. Baltimore. Williams & Wilkins Company, 1937.

Many new books on dietetics have appeared recently, and one naturally looks for some distinctive quality in each. The outstanding character of Miss Stern's work at the Boston Dispensary is well known, and this is reflected in the book, which is one of the few on dietetics that takes up in detail the problem of "getting the diet over to the patient." In addition the usual material on dietetics and food values is well presented in brief form.

Original Papers of Richard Bright on Renal Disease. By A. Arnold Osman, D.S.C., F.R.C.P. Price, \$7.25. Pp 172. London. Oxford University Press, 1937.

This is a beautiful reprinting of the papers by Richard Bright on renal disease. As a result of Bright's presentation on the subject of renal disease, the medical profession first began to differentiate various types of dropsy. The contributions of this truly great man in 1827 were fundamental, and therefore the book is of tremendous historical value. It should be in the library of any physician at all interested in the development of medicine.

Internal Diseases of the Eye and Atlas of Ophthalmoscopy. By Manuel Uribe Troncoso. Price, \$15. Pp 530, with 239 figures (82 color plates). Philadelphia. F. A. Davis Company, 1937.

The reviewer is not an ophthalmologist, but to him this book seems extremely useful. Its main feature is the numerous diagrams and color plates of eyegrounds in conditions both normal and pathologic. The text is brief and seems to be intended mainly to explain the plates.

Lehrbuch der Elektrokardiographie. By Dr. D. Scherf. Price, 16.50 marks. Pp 241, with 169 illustrations. Wien. Julius Springer, 1937.

This excellently printed and well illustrated monograph covers adequately the subject of clinical electrocardiography and the principal cardiac arrhythmias. Nothing essentially new, however, is added to the material found in the many books on the same subject which have recently appeared.

ARCHIVES of INTERNAL MEDICINE

VOLUME 61

MARCH 1938

NUMBER 3

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RELIEF OF DIABETIC PAIN OF NEUROCIRCULATORY ORIGIN BY ORAL ADMINISTRATION OF SODIUM CHLORIDE

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In a previous paper one of us¹ presented certain observations indicating that the pain of diabetic neuritis was relieved temporarily by the oral administration of sodium chloride in amounts ranging from 15 to 90 Gm daily over periods of two to four weeks with interruptions of ten to fourteen days. It appeared likely that the relief thus obtained was due to a vasodilating effect of the sodium chloride. The present study was undertaken primarily for the purpose of studying the effect of this salt on a larger series of diabetic patients complaining of pain who had not been relieved by the usual diabetic management.

METHOD

Thirteen patients with pain of either neuritic or vascular origin were studied. For the purpose of study the patients were divided into three groups: first, a group of seven patients in whom definite neurologic signs were found, consisting of hyporeflexia, areflexia and sensory changes; second, a group of three patients whose chief symptoms were severe arteriosclerosis and its sequelae; third, a group of three patients in whom objective neurologic signs were not found and whose arteriosclerosis would not ordinarily be considered significant.

All these patients were observed for a control period of two weeks or longer. Eight of them were purposely given an inadequate amount of insulin in order to permit observation of the effect of sodium chloride on the level of the blood sugar. The remaining five patients were given a sufficient amount of insulin to maintain a satisfactory blood sugar level.

A determination of the blood sugar level was made twice weekly during fasting and at 11 a m and at 2 30 p m at least once weekly in all cases except for two outpatients, for whom three determinations were made at intervals of about two weeks. The other laboratory procedures included determinations of the values for serum calcium, blood chloride, plasma cholesterol and urinary chloride,

¹ Sandstead, H R. The Effects of the Oral Administration of Sodium Chloride in Diabetes, *Hosp News* 3 21 (Nov 1) 1936.

renal function tests, Wassermann tests of the blood and the usual examinations of the blood and urine made as a routine

The cutaneous histamine reaction, as described by de Takats,² was tested in seven of the patients before and after the administration of salt. Roentgen examinations of the legs were made as a routine to determine whether calcification of the arteries was present.

The same method of administration of the salt was used as in the previous study.¹ Briefly, it was as follows: The salt was given in solution three or four times daily and was sipped over a period of half an hour. The dose given daily was 0.25 to 0.5 Gm per kilogram of body weight. This was found to be the maximum dose not causing any gastric disturbance. In order to relieve the monotony of taking the salt and to prevent possible untoward effects, the salt was given for interrupted periods of two to four weeks over periods ranging from one to twelve months.

OBSERVATIONS

Group 1 Patients in Whom Definite Neurologic Signs Were Found—In this group of seven patients there were five who could be classed as having severe diabetes and two who could be classed as having mild diabetes. The ages ranged from 37 to 65 years, and the known duration of the diabetes was from two and one-half to twelve years. All the patients had peripheral neuritis. In four the symptoms appeared at the onset of the diabetes, and in three they appeared one and one-half to six years after the onset. All continued to have neuritic pain in spite of the treatment for diabetes. The chief symptoms were pain, hyperesthesia and muscular weakness. The objective neurologic signs consisted of absence of the achilles tendon reflexes in all the patients, absence or diminution of the knee jerks in six, absence of the reflexes in the upper extremities of three and absence of the vibratory sense in the lower extremities of two. The site of the neuritis was limited to the lower extremities in five patients, in one patient the neuritis involved the entire body and in one it involved both upper and lower extremities. Vascular disease was present to some degree in all the patients, as noted in table 1. The degree of arteriosclerosis was determined by palpation of the peripheral arteries, ophthalmoscopic and roentgen examinations and histamine tests. There were four patients in this group who showed calcification of the peripheral arteries roentgenographically and four without pulsation of the dorsalis pedis arteries.

The patients in this group have been under observation for two and one-half to twenty-four months and have received sodium chloride orally over interrupted periods of one and one-half to twelve months. Three of the patients obtained complete relief from pain, and four obtained marked relief. There was definite improvement in the circulation of three on

² de Takats, G. The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, *Arch Int Med* **48** 769 (Nov.) 1931.

whom the cutaneous histamine test was performed, as shown by the increase in the response, and in two of four patients evidence of improvement was shown by the return of the pulsations of the dorsalis pedis arteries. No changes were observed in the objective neurologic signs after the administration of salt.

The case of B. J., a woman with neuritis of nine years' duration, is of particular interest in that she has been treated as an outpatient, receiving orally 20 to 24 Gm of sodium chloride for interrupted periods of two to three weeks for the past

TABLE 1—*The Effect of the Oral Administration of Sodium Chloride on Neuritic Patients with Definite Neurologic Signs**

Patient	Age, Years	Control Period								Period of Administration of Salt			
		Duration of Diabetes, Years	Duration of Pain, Yr	Diabetes	Pain	Degree of Arterio sclerosis	Average Blood Sugar Value (Fasting), Mg per 100 Cc	Units of Insulin Daily	Histamine Test Before Administration of Salt	Sodium Chloride, Gm Daily	Length of Time Salt Was Administered, Mo	Histamine Test After Administration of Salt	Relief of Pain
W. C.	47	2½	1	Severe	Severe	3	140	40	1	20	1½	2	Marked
S. G.	40	2½	2½	Moderate	Severe	2	195	20	1	28	3	3	Complete
W. L.	37	5	5	Severe	Severe	2	367	70		11 to 16	5		Marked
B. J.	44	12	9	Severe	Severe	3	339	60	1	20 to 40	1	3	Marked in hands, complete in lower extremities
A. R.	65	5	5	Severe	Moderate	4	256	65		20	4		Marked
E. H.	38	2½	2½	Severe	Moderate	2	245	124		60 to 30	12		Complete
W. M.	60	8	2	Moderate	Severe	4	248	0		30 to 16	6		Complete

* In tables 1 to 3 the degree of arteriosclerosis is designated as follows: 1 indicates mild, 2, moderate, 3, moderate, with roentgen evidence of calcification in the vessels of the legs, and 4, severe, as shown by extensive calcification. The response to the cutaneous histamine test is shown as follows: 0 indicates no response, 1, faint, 2, fair, and 3, marked reactions.

four months. Progressive improvement in the relief of pain has been obtained during the past three months. This is the first time in nine years that she has been completely free from pain in the lower extremities, and for the first time in several winters she has not required extra protection of the feet at night for warmth. There has also been considerable relief of pain in the hands. The pulsations of the dorsalis pedis arteries are again palpable.

The following case report illustrates the effect of salt on neuritic pains which had caused complete disability.

W. C., a man aged 47 years with diabetes of two and one-half years' duration, was admitted to the hospital on Dec. 11, 1936, because of burning pain over the

entire body, most marked in the feet and legs, weakness, loss of weight and poor appetite. Neuritic symptoms had appeared about one year before and had become progressively more severe. He had been on a diet containing 235 Gm of carbohydrate, 77 Gm of protein and 90 Gm of fat and had been taking a total of 78 units of insulin daily.

Examination revealed a poorly nourished man, weighing 103 pounds (47 Kg). There was arteriosclerosis of grade 3. The dorsalis pedis and posterior tibial arteries could not be palpated. There was hyperesthesia over the entire body, it was so marked in the lower extremities that the patient could not tolerate the touch of bedclothes. The only other neurologic finding was absence of the achilles tendon reflexes. During the control period he was on a diet containing 150 Gm of carbohydrate, 70 Gm of protein and 80 Gm of fat and received a total of 40 units of insulin daily. The blood sugar value was maintained at an average fasting level of 140 mg. Although the diabetes was well controlled, it was necessary for him to remain in bed on account of the neuritic symptoms.

The period of interrupted oral administration of salt began on Jan 6, 1937. He was given 20 Gm daily for the remainder of the month. The dosage of insulin was not changed, and the diet was increased without elevation of the blood sugar level. By the end of this period the pains were minimal. Administration of salt was resumed on February 15 and was continued until March 1, at which time the patient had only an occasional pain. He had gained 7 pounds (3 Kg), there was less weakness and he was active about the ward. The diet had been increased to 200 Gm of carbohydrate, 76 Gm of protein and 86 Gm of fat, without changing the dosage of insulin, and the blood sugar level was not elevated.

Before admission to the hospital this patient had been receiving an adequate diet, and the diabetes had been controlled with large doses of insulin. During the initial period after his admission to the hospital the blood sugar level was maintained at 140 mg. However, during this time he obtained no relief from the neuritic symptoms. It was only after the administration of sodium chloride that these symptoms disappeared. This is good evidence that neither hyperglycemia nor vitamin deficiency was responsible for the neuritis.

What was true in this case was true for the entire group. After the administration of sodium chloride it was possible to increase the diet and to reduce the dosage of insulin and at the same time to maintain the blood sugar level or reduce it for all the patients except one, whose insulin requirement was increased with the increase in diet. It appeared at first that the increase in diet might be a factor in relieving the neuritic symptoms, but there was no constant relation between the improvement of the symptoms and the increase in diet.

Group 2 Patients with Severe Arteriosclerosis—Three patients are included in this group (table 2). All of them had severe arteriosclerosis without objective neurologic changes. Their diabetes was easily controlled with small amounts of insulin. In each instance the diet was increased, and the dosage of insulin was reduced when salt was given.

F. H. K. had had an amputation of the left leg for gangrene one year prior to the present admission to the hospital and had a painful, cold, cyanotic foot. After six months of interrupted administration of salt the pains were completely relieved, the foot was warm and its color was good.

C S had had an amputation for gangrene several months before the present admission to the hospital. The remaining leg was cold and moderately painful. After the administration of 18 Gm of salt daily for twenty days the leg was warm and the pains had disappeared. Three weeks after discontinuance of the salt therapy he died as the result of a mycotic aneurysm of the left femoral artery and myocardial infarction.

The following case is reported in detail because it shows the remarkable effect that sodium chloride had on the course of the disease.

M F, a man aged 66 years with diabetes of four years' duration, was admitted on May 18, 1936, because of deep burning and cramping pain of the feet and legs which had been present for about three years. He had not been on a rigid diet and was taking 20 units of insulin daily. He had glaucoma six months before entry into the hospital.

TABLE 2—*The Effect of the Oral Administration of Sodium Chloride on Diabetic Patients with Pains of Arteriosclerotic Origin*

Patient	Age, Years	Duration of Diabetes, Years	Duration of Pain, Yr	Control Period						Period of Administration of Salt				
				Diabetes	Pain	Degree of Arterio-sclerosis	Average Blood Sugar Value (Fasting) Mg per 100 Cc	Units of Insulin Daily	Histamine Test Before Administration of Salt	Sodium Chloride, Gm Daily	Length of Time Salt Was Administered	Histamine Test After Administration of Salt	Relief of Pain	
C S	68	19	4	Moderate	Moderate	4	142	15	2	18	20 da	3	Complete	
F H K	65	4	2	Moderate	Severe	4	253	40	1	14	6 mo	3	Complete	
M F	66	3	3	Moderate	Severe	4	153	15	0	42 to 21	5 mo	2	Complete	

Examination revealed a moderately obese elderly man, weighing 213 pounds (96.6 Kg), who appeared chronically ill. The essential findings were arteriosclerosis of grade 4, absence of pulsation in the dorsalis pedis and posterior tibial arteries and moderate hypertrophy of the left ventricle. There was choroidal and retinal arteriolar sclerosis of grade 3, with numerous small hemorrhages disseminated over the fundi. There was a negative response to the histamine flare test on the knees.

For a control period of two weeks he was placed on a diet containing 150 Gm of carbohydrate, 70 Gm of protein and 80 Gm of fat, with 15 units of insulin daily, without improvement of the pain. During this period the blood sugar was maintained at a satisfactory level. The use of insulin was discontinued, and the patient was given 42 Gm of sodium chloride daily the first two weeks, 21 Gm daily the third week and 42 Gm daily during the fourth week. During this period the blood sugar was maintained at approximately the same level as during the control period. Three weeks after the administration of sodium chloride was started the pains in the legs were much relieved, and the patient was taking short

walks After a rest period of two weeks he was again given 21 Gm of salt daily for two weeks He was completely relieved of the pain in the legs and feet by the end of this period

Histamine flare tests on July 13 showed a fair response During this period there was a recurrence of glaucoma in each eye Operations for relief of this condition were unsuccessful He was not given sodium chloride again for four months Two months after discontinuing the use of sodium chloride he again complained of increasing pain in the feet One month later large bullae appeared on the great toes, there was an indolent ulcer on the heel of the left foot and the pains in the legs were severe The ulcer increased to 2 by 2 cm in diameter, and the distal third of the affected toes became black He was again given 21 Gm of sodium chloride daily for three weeks By the end of this period the necrotic crust had sloughed, and epithelization was nearly complete The ulcer showed signs of healing, and the pains were minimal Treatment with sodium chloride was discontinued because of slight edema of the ankles After a three weeks' rest period he was again started on 21 Gm of salt, and this was continued for two weeks By the end of this period the lesions were completely healed, the pulsations of the dorsalis pedis arteries were palpable and he was free from pain

The relief of symptoms and the improvement in the circulatory changes after the administration of sodium chloride in this group of patients are striking All of them obtained complete relief from pain and definite improvement in the circulation, as shown by the change in color and the increase in temperature of the feet and by the response to the histamine test

Group 3 Patients with Neuritic Pains in Whom Neurologic Signs Were Not Found—Three patients are included in this group (table 3)

O R, whose pain was mild, may have been relieved by control of the diabetes However, this patient had been taking 70 units of insulin while on a diet containing 150 Gm of carbohydrate, 70 Gm of protein and 80 Gm of fat After several months of interrupted administration of sodium chloride the pains were completely relieved, the dosage of insulin was reduced to 35 units daily and the diet was increased to 200 Gm of carbohydrate, 70 Gm of protein and 200 Gm of fat

R M, whose diabetes was under good control without improvement in the pain during the preliminary period, was completely relieved one month after the administration of salt was started The dosage of insulin was reduced in this instance from 55 to 38 units, the diet remaining unchanged Two months after discharge he reported that the pains had not returned

The following case is reported in detail because it shows that some factor other than hyperglycemia is responsible for pain

L H, a man aged 41, with diabetes of fourteen years' duration, was admitted to the hospital on Dec 3, 1936, complaining of drowsiness, pain over the entire body but most marked in the feet, legs and arms, and loss of weight and strength The neuritic symptoms were of about eight months' duration He had been in diabetic coma nine times in the past six months He had not been rigidly following a diet, and he was taking 24 units of insulin daily

Examination revealed a moderately undernourished man, weighing 136½ pounds (62 Kg), with acidosis The remainder of the physical examination disclosed nothing of importance except mild arteriosclerosis

During the control period he was on a diet containing 150 Gm of carbohydrate, 70 Gm of protein and 80 Gm of fat, with a total of 40 units of insulin daily. The acidosis disappeared within a few days, but the blood sugar level remained elevated, averaging 329 mg during fasting. The initial period of interrupted oral administration of salt began on December 18 and continued until Jan 2, 1937, 30 Gm being given daily. The average blood sugar value during fasting was reduced by 65 mg during the period, without change in the dosage of insulin. He stated that the pains had diminished slightly. After the discontinuance of treatment with sodium chloride the blood sugar returned to the previous level in spite of an increase in the dosage of insulin by 10 units. The second period of administration of salt was begun on January 13 and continued until January 25, 20 Gm being given daily. During this period the diet was increased to 175 Gm of carbohydrate, 76 Gm of protein and 106 Gm of fat. During fasting the blood sugar value averaged 304 mg. The hyperglycemia may be explained in part by

TABLE 3—*The Effect of the Oral Administration of Salt on Neuritic Patients Without Objective Neurologic Signs*

Patient		Age, Years	Control Period						Period of Administration of Salt					
			Duration of Diabetes	Duration of Pain, Mo	Diabetes	Pain	Degree of Arterio sclerosis	Average Blood Sugar Value (Fasting), Mg per 100 Cc	Units of Insulin Daily	Response to Histamine Before Administration of Salt	Sodium Chloride, Gm Daily	Length of Time Salt Was Administered	Response to Histamine After Administration of Salt	Relief of Pain
O	R	34	14 mo	14	Severe	Mild	1	252	70		26	3 mo		Complete
L	H	41	14 yr	8	Severe	Severe	1	329	40	2	30 to 20	5 wk	3	Complete
R	M	46	11 yr	2	Moderate	Severe	2	164	55		30	1 mo		Complete

acute nasopharyngitis. The pain gradually disappeared, and by the end of the period he had only an occasional shooting pain in the legs.

After discontinuance of treatment with salt he was given a long "rest period," which lasted until March 11. During this period the diet was increased to 200 Gm of carbohydrate, 76 Gm of protein and 106 Gm of fat. The dosage of insulin was increased to 60 units daily in order to keep the blood sugar at a satisfactory level. The pains increased and were as severe as when he was admitted to the hospital. The administration of sodium chloride was resumed on March 11 at his request and was continued for the remainder of the month. During this period he received 20 Gm daily, and the dosage of insulin was reduced by 10 units. The blood sugar level was not elevated above that of the previous month, and the patient was completely relieved of pain.

When this patient was admitted to the hospital he was in diabetic acidosis, therefore, dehydration must be considered as a factor in producing the neuritic pains. However, after he was given sufficient fluids and the acidosis had disappeared he continued to have the neuritic symptoms, which were relieved with sodium chloride. While he was taking sodium chloride, the pains ceased even though the blood sugar level

was elevated, and when it was discontinued the pains returned in spite of a satisfactory blood sugar level. Hyperglycemia appeared not to be a factor in causing the neuritic pains.

COMMENT

We have presented observations on thirteen diabetic patients with pains which may be classed as of neuritic origin in ten (groups 1 and 3) and of vascular origin in three. The pains in most of the cases had been of long duration and had persisted in spite of treatment for the diabetes. All the patients received marked to complete relief of the pains after oral administration of sodium chloride. The patients with severe arteriosclerosis showed, in addition to the relief of pain, definite signs of improvement in the vascular disease, as evidenced by the healing of gangrenous toes and of an indolent ulcer and by changes in the color and temperature of the feet. In the group of patients with neuritic pains the only change noted in addition to the relief of pain was the increase in response to the histamine test, indicating improvement in the circulation after administration of sodium chloride. In these two groups the relief of pain appeared to be accompanied with signs of improvement in the circulation. This suggests that ischemia, the result of vascular disease, may be the cause of the neuritic symptoms.

This study raises the question as to the possible etiology of diabetic neuritis, which has long been a subject of considerable controversy. Jordan³ has made an extensive review of the literature and has reported his observations on a group of two hundred and twenty-six patients with diabetic neuritis. He placed his patients in four groups, according to whether they had hyperglycemic, circulatory, degenerative or neuritic disorders. Those with hyperglycemia presented no factor except hyperglycemia to explain the neuritis. Only thirty-four patients were placed in this group. Over 95 per cent of the patients in the other groups had evidence of vascular disease, which, he pointed out, may be a factor in causing the neuritis.

It has already been mentioned that neither hyperglycemia nor vitamin deficiency appeared to be responsible for the neuritic symptoms of any of our patients. Foci of infection were found in a few instances, however, no treatment was given for these conditions until after relief of the neuritis had been obtained with sodium chloride. There were no other possible causes of neuritis found, such as anemia, metal poisoning or alcoholism. The Wassermann reaction of the blood was negative in all the cases, and there was no clinical evidence of syphilis to explain the neurologic findings.

3 Jordan, W. R. Neuritic Manifestations in Diabetes Mellitus, *Arch Int Med* 57:307 (Feb) 1936.

We have not studied a sufficient number of cases to draw any definite conclusions, but the fact that both the patients with neuritic pain and those with severe arteriosclerosis obtained relief from pain, accompanied with signs of improvement in the circulation, is evidence that ischemia, the result of vascular disease, primarily arteriosclerosis, is the probable cause of the neuritic symptoms. This view is in agreement with that of Woltman and Wilder,⁴ who, in a comprehensive study of this problem, have pointed out that neuritis commonly occurs in patients whose diabetes is under control, that is, in patients who are free from either acidosis or glycosuria. They reported ten cases of neuritis in which autopsy showed a certain amount of arteriosclerosis of the intraneural vessels. This they considered consistent with the idea of ischemia of the nerves as a factor in the neuropathy.

The improvement observed in the vascular disease of our patients after the oral administration of sodium chloride is in accord with the observations of Perlow,⁵ who found that certain types of vascular disease in nondiabetic patients were benefited by treatment with hypertonic solution of sodium chloride intravenously, and also those of de Takáts,⁶ who has recommended the oral administration of sodium chloride for occlusive vascular disease.

In view of our findings and those just cited it seems that the oral administration of sodium chloride is rational therapy for the neurocirculatory complications of diabetes.

We are not able to offer an explanation for the action of sodium chloride in producing the circulatory changes which have been observed in patients with vascular disease. The chemical studies of the blood, which included analyses of the chloride, calcium and cholesterol contents, did not show any change after the administration of sodium chloride. The determinations of the chloride content of the urine showed the output of chloride to be increased in proportion to the amount given. Only two of the patients showed slight edema of the lower extremities, and no constant change was noted in the weight as a result of the administration of salt. No impairment of renal function was found after the administration of sodium chloride, nor was there evidence of any other ill effects.

4 Woltman, H. W., and Wilder, R. M. Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch Int Med* **44** 576 (Oct) 1929.

5 Perlow, S. Conservative Treatment in Occlusive Vascular Diseases of the Extremities, *Ann Int Med* **8** 741 (Dec) 1934.

6 de Takáts, G. Peripheral Vascular Disease. Its Significance for General Practitioners and Specialists, *J A M A* **104** 1463 (April 27) 1935.

SUMMARY AND CONCLUSIONS

Observations have been made, before and after the oral administration of sodium chloride, on thirteen diabetic patients, with pain of neuritic origin in ten and with pain of arteriosclerotic origin in three.

All the patients obtained complete or marked relief of the neuritic symptoms after the administration of sodium chloride.

The relief of pain was accompanied with signs of improvement in the vascular disease in the patients with arteriosclerotic pain and with improvement in the circulation of those with neuritic pain, as shown by the histamine test.

The observations made in this study indicate that ischemia, the result of vascular disease, primarily arteriosclerosis, is responsible for the neuritic symptoms.

In view of our findings the oral administration of sodium chloride appears to be the rational treatment for the neurocirculatory complications of diabetes.

The members of the staffs of the Cleveland City, Lakeside, St. Alexis and St. Luke's hospitals cooperated in furnishing us patients for this study.

ELECTROCARDIOGRAPHIC PATTERNS IN ACUTE PERICARDITIS

EVOLUTION, CAUSES AND DIAGNOSTIC SIGNIFICANCE OF PATTERNS IN LIMB AND CHEST LEADS, A STUDY OF FIFTY-SEVEN CASES

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AND

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From time to time various changes have been shown to develop in the electrocardiograms of patients with acute pericarditis¹ Often these have been striking, consisting in the main of diminished amplitude of the ventricular complex in the presence of effusion, inversion of the T wave and elevation of the RST segment In studying fifty-seven cases of acute pericarditis of different etiologic types we encountered changes of this type sufficiently often to lead us to feel that striking alterations of the electrocardiogram frequently develop in cases of acute pericardial disease and that in a certain percentage of cases they may assume a pattern that is distinctive enough to have diagnostic value In the present paper we wish to describe these changes and to discuss their cause

MATERIAL

The varieties of pericarditis represented in our series of fifty-seven cases were varied and included the following etiologic types rheumatic pericarditis (thirteen cases), pneumococcal pericarditis (six cases), uremic pericarditis (five cases),

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1 (a) Harvey, J, and Scott, W Changes in the Electrocardiogram in Course of Pericardial Effusion with Paracentesis and Pericardiotomy, *Am Heart J* **7** 532, 1932 (b) Oppenheimer, B S, and Mann, H An Electrocardiographic Sign in Pericardial Effusion, *Proc Soc Exper Biol & Med* **20** 431, 1923 (c) Porte, D, and Pardee, H E B The Occurrence of Coronary T Wave in Rheumatic Pericarditis, *Am Heart J* **4** 584, 1929 (d) Purks, W K The Occurrence of a Coronary T Wave in Purulent Pericarditis, *South M J* **24** 1032, 1931 (e) Scherf, D Ein elektrokardiographisches Zeichen bei Erguss in Herzbeutel, *Wien klin Wchnschr* **43** 298 (March 6) 1930 (f) Schwab, E H, and Herrmann, G Alterations of the Electrocardiogram in Diseases of the Pericardium, *Arch Int Med* **55** 917 (June) 1935 (g) Scott, R W, Feil, H, and Katz, L N The Electrocardiogram in Pericardial Effusion Clinical, *Am Heart J* **5** 68, 1929

hematopericardium (rupture of an aneurysm, one case, stab wound, two cases), neoplastic pericarditis (two cases), pericarditis due to staphylococcic septicemia (one case), tuberculous pericarditis (twenty cases) and pericarditis of unknown etiology (seven cases)

The clinical diagnosis was confirmed by necropsy in twenty-two cases, by surgical intervention in four cases and by paracentesis in four additional cases. In the remainder of the fifty-seven cases characteristic clinical and roentgen findings established the diagnosis, in our opinion, beyond reasonable doubt, these usually included the demonstration of a friction rub or the presence of a characteristic fluoroscopic silhouette

ELECTROCARDIOGRAPHIC FINDINGS

The incidence of electrocardiographic changes was as follows. No alterations were seen in twelve cases, definite abnormalities were present in forty-five. We have considered as definite abnormalities unmistakable deviation of the RST segment in one or more limb or chest leads (twenty-six cases) and definite inversion of the T wave (nineteen cases). We also encountered a ventricular complex of low amplitude in seventeen of our fifty-seven cases and interesting types of auricular arrhythmia, including extrasystoles, flutter and fibrillation in six additional cases. Because these abnormalities commonly occur in association with other forms of cardiac disturbances, we have not included them among the abnormal findings and shall not consider them further.

Deviation of the RST Segment—Among previous observers, Schwab and Herrmann^{1†} alone made use of chest leads. They applied this method in only two cases and concluded that it furnished no information of differential diagnostic value. We used three chest leads² as well as three limb leads in all but five of the twenty-six cases listed in which there was deviation of the RST segment and found that their use frequently gives information of importance. Often they exaggerate deviation of the RST segment that is present but inconspicuous in limb leads, or they reveal deviation which is not shown in limb leads.

Alterations of the RST segment may be really striking, and in the combined limb and chest leads they may assume a pattern which we have not encountered in association with any condition but acute peri-

2 Throughout our studies the precordial leads were applied in the manner previously described (Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C. Further Observations on the Use of Direct Chest Leads in Coronary Occlusion, *Arch. Int. Med.* **52**: 752 [Nov.] 1933). Lead IV was obtained by placing the right arm electrode over the cardiac apex and the left arm electrode at the angle of the left scapula. In lead V the right arm electrode was placed at the apex, the left leg electrode, on the customary site. In obtaining lead VI the left arm electrode was placed at the angle of the left scapula, the left leg electrode, in its normal position.

carditis. The important features of this pattern are (1) elevation of the RST segment in leads I to III or in leads I and II alone, (2) depression of the RST segment in leads IV and V, with a well preserved initial downward deflection, (3) elevation of the RST segment in lead VI, even when there is no elevation in lead III³.

In our experience this combination of findings is not uncommon in cases of acute pericarditis. In twenty-one of the forty-five cases in which there were definite abnormalities this pattern was strictly complied with, in three additional cases in which direct leads were not used the indirect leads were characteristic.

The relative frequency of these characteristic findings indicates that they may possess some diagnostic importance, we have not so far encountered them exactly in association with any other condition, though we are not prepared to say that they may not so occur. In certain instances of occlusion of the anterior coronary artery the electrocardiographic findings are similar, but there are as a rule certain definite differences, which will be discussed later.

Alteration of the RST segment in cases of pericarditis is a transient and frequently brief phenomenon. We have never observed it to persist in the limb leads for more than twelve days. The detection of these changes, therefore, is not to be expected unless tracings are obtained frequently. The chest leads continued to show deviations for several days, as a rule, after they had disappeared from the limb leads.

Since deviations in the RST segment are of brief duration and since they do not disappear simultaneously⁴ from individual leads, one can expect to encounter tracings in which perhaps striking changes were present in one or more limb or chest leads, with slight or no changes in the other leads (fig 2 *A* and *C*). In three additional cases of our series these findings were noted. Although in such cases the pattern is not strictly complied with, these isolated changes if they are marked may still be suggestive of pericarditis and are therefore of some importance.

In some of our cases of pericarditis in which deviation in the RST segment was not noted either in the limb or in a conventionally placed precordial lead, we discovered that modifying the usual chest lead by placing the anterior electrode over the area of friction not infrequently revealed these alterations. In two cases of tuberculous pericarditis in which the electrocardiograms showed no deviation in the RST segment in either the limb or the customary precordial lead, definite

3 Elevation of the RST segment in all three leads may occur even in the presence of left axis deviation (fig 5).

4 The deviations in the RST complex usually disappear first from the leads in which they are least marked in the initial tracing.

alterations were brought out by this maneuver. In four other cases deviation in the RST segment in the usual chest lead was definitely exaggerated when the electrode was placed over the area of friction (fig 4).

Striking deviations in the RST segment were encountered in the electrocardiograms of patients with all the varieties of acute pericardial disease represented in our series (table 1). They develop most readily apparently in association with the pneumococcic type, they were infrequent in cases of the tuberculous variety. This difference in incidence will be discussed later.

TABLE 1—*Electrocardiographic Changes Associated with Pericarditis**

Etiologic Factor	Total Num ber of Cases	Deviation in RST Segment, Limb Leads		RST Segment in Precordial Leads		Change in T Wave Only	Nega tive Find ings	Died	Ne cropsy	Opera tion
		I to III	I and II	Depres sion IV and V	Eleva tion VI					
Rheumatic pericarditis	13	5	3	7	6	2	3	3	1	1
Pneumococic pericarditis	6	4	2	6	6			6	5	2
Uremic pericarditis	5	2		3	2	1	1	5	4	
Hematopericardium	3	2		1	Not done	1		2	1	
Neoplastic pericarditis	2		1	1	1		1	1	1	
Pericarditis due to staphylococ ic septicemia	1		1	Not done	Not done			1	1	
Tuberculous pericarditis	20	1	1	1	1	12	5	12	7	1
Pericarditis of unknown origin	7	2		3	3	3	2	4	2	
Total	57	16	8	22	19	19	12	34	22	4
		24								

* In three of the twenty four cases in which there was deviation of the RST segment in the limb leads, no precordial lead was made, in one case there was no change in the precordial leads, and in three cases no deviation was observed in lead VI. In two additional cases a deviation in the RST segment was observed in the precordial and not in the limb leads.

Changes That Succeed Deviation of the RST Segment—Since deviation of the RST segment is transient and of brief duration, the changes that succeed it are of interest. The usual development in the limb leads, as shown in fifteen cases, is a gradual return of the RST segment toward the base line. When this is nearly complete the upright T wave begins to show a dip downward in its terminal portion and finally becomes frankly inverted and usually cove-shaped. This may occur in all three leads if the RST segment is initially elevated in all leads, it involves leads I and II only when the RST segment is affected in only these leads. If recovery occurs, this configuration, after persisting for a variable time, may become entirely normal.

Occasionally the T wave of the indirect leads never becomes inverted, but assumes its normal configuration as the deviated RST segment returns to the iso-electric line. We observed this behavior in three cases.

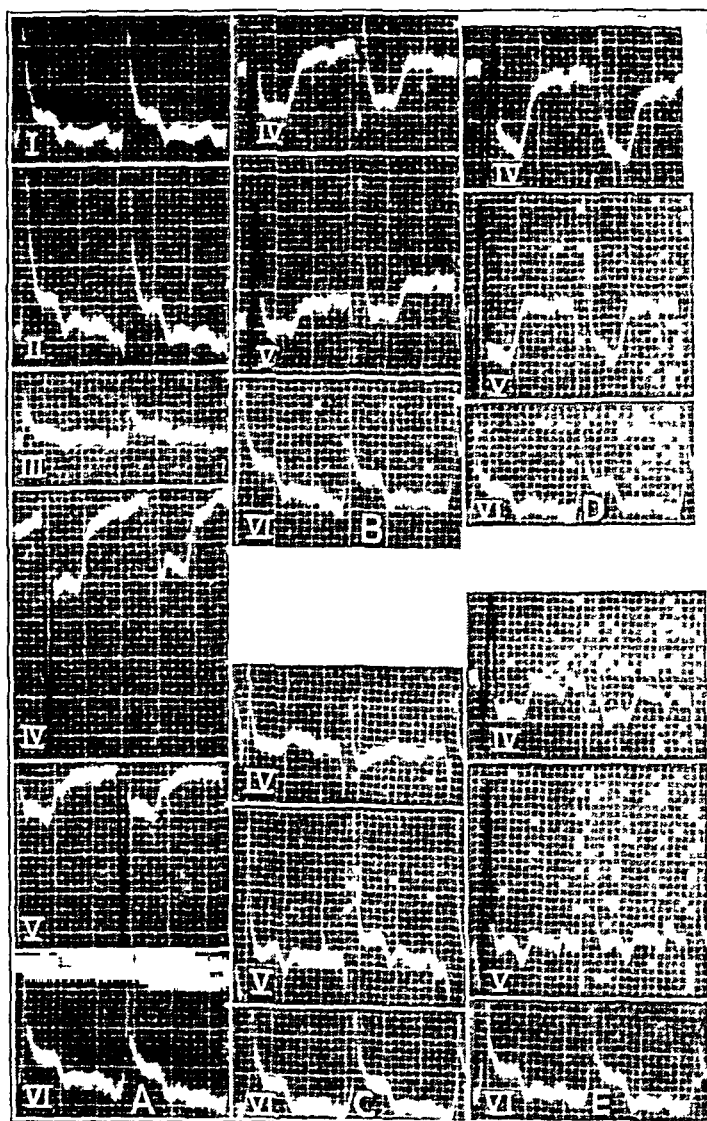


Fig 1—Electrocardiograms of a patient aged 48 with pneumococcic pericarditis. Postmortem examination revealed a purulent exudate, with little fluid present in the pericardial sac. Microscopic study revealed infiltration of the inflammatory process into the epicardial portion of the myocardium (fig 8). All the tracings were made on Feb 20, 1935. *A*, note the elevation of the RST segment in leads I to III and the marked depression, with preservation of the initial downward deflection, in leads IV and V, with elevation of the RST segment in lead VI. *B*, the anterior electrode was placed over the third interspace to the left of the sternum, *C*, over the base, *D*, over the lower portion of the sternum, and *E*, over the fifth interspace to the right of the sternum. Note that deviation of the RST segment is present in *B*, *C*, *D* and *E* and that the algebraic summation of the deviations of the RST segment in leads IV and VI is approximately equal to those of lead V.

In six of our cases a peculiar type of inversion of the T wave was noted in limb leads as an intermediate stage between the elevated RST and the common type of inverted T wave. Taking origin at or slightly above the iso-electric line, the gradual more or less normal upstroke of the T wave is followed by a sharp, beaklike downward dip, which inverts the terminal portion of the T wave. The T waves which are

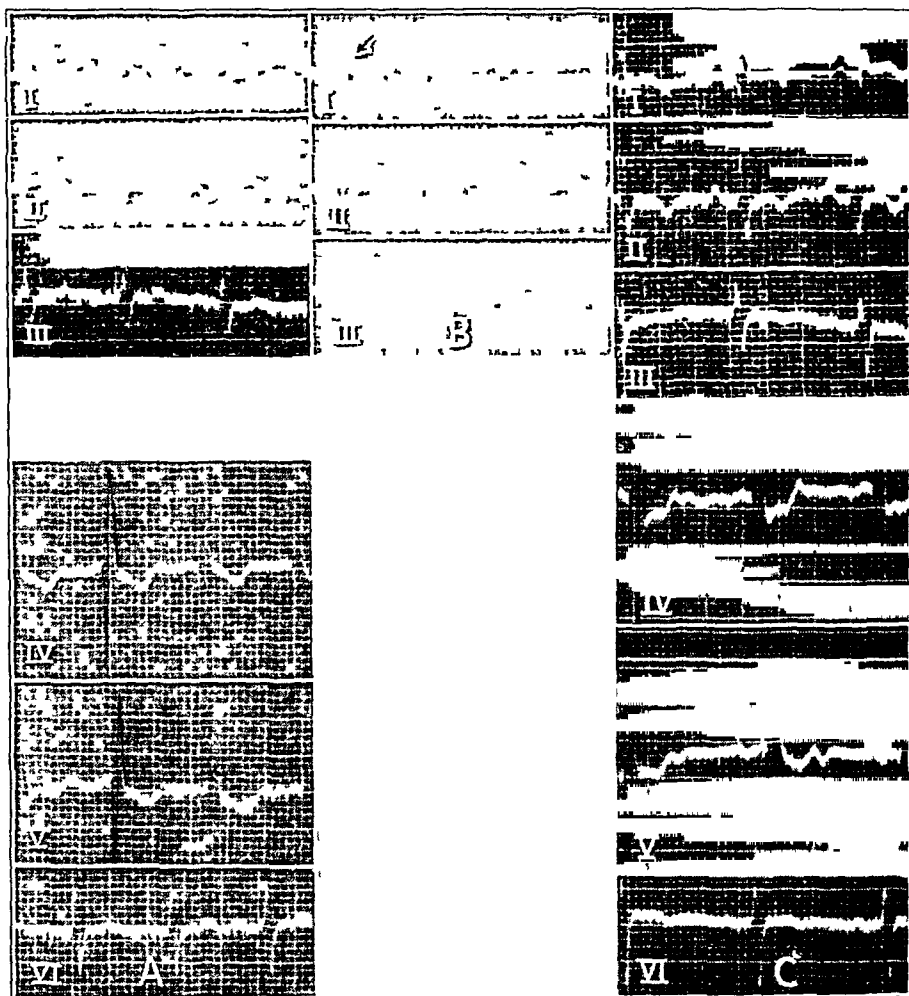


Fig 2—Tuberculous pericarditis. *A*, June 24, 1936. Note the elevation of the RST segment in lead I, leads IV and V show a slight depression, lead VI is normal. *B*, July 6, 1936. Note the inverted T_1 wave and the slightly inverted T_2 wave, with the peculiar type of T wave in lead I (described in text). *C*, July 23, 1936. The T wave is inverted in leads I and II. Note the slight depression of the RST segment in lead IV and none in lead V, with maintenance of the initial downward deflection.

shown in figure 2 *B* were also observed by Schwab and Herrmann in cases of pericarditis. This type of T wave by itself is not characteristic of the changes produced by pericarditis since we have observed it in

association with other conditions. However, when this wave is preceded by a suggestive elevation in the RST segment and accompanied with changes in the precordial leads which conform with the pattern described, it represents a suggestive sign of pericarditis.

The developments that succeed depression of the RST segment of chest leads usually run parallel to those seen in limb leads. They are of some added importance because of their persistence, alterations may still remain after they have disappeared from the limb leads.

Alterations of the T Wave Alone—In the nineteen cases the only electrocardiographic changes seen in limb leads in our initial studies consisted of flattening or inversion of the T wave in lead I or in leads

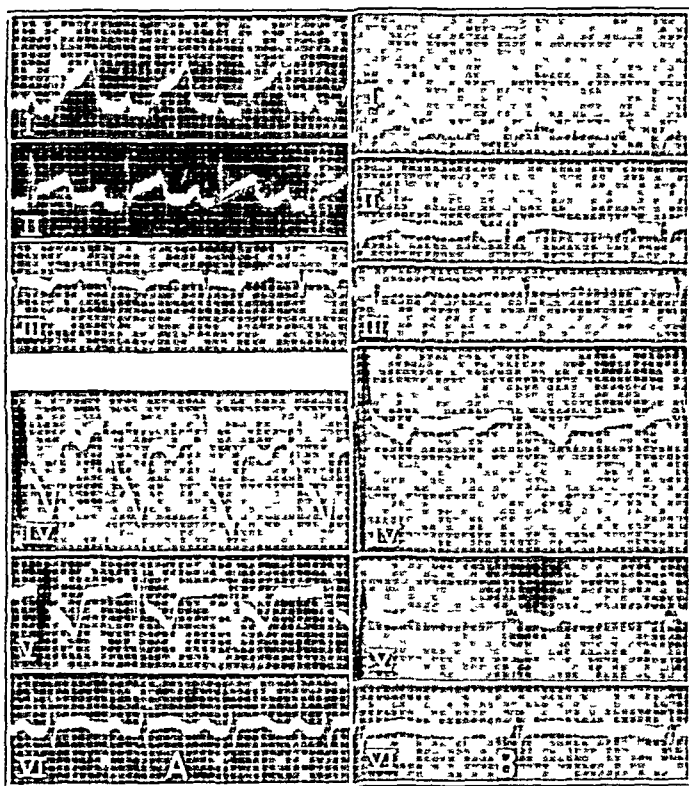


Fig 3—A man aged 38 was admitted to the hospital on Aug 2, 1936, complaining of fever, cough and severe precordial pain. Among other possibilities, coronary occlusion was suspected, and an electrocardiogram was taken. A pericardial friction rub was heard after the electrocardiogram was taken and was suggestive of pericarditis. This patient made a complete recovery and was able to return to his former occupation as a policeman without cardiac symptoms. In view of the typical electrocardiographic pattern—similar to that associated with proved pericarditis, the electrocardiographic changes were considered to be secondary to pericarditis (unknown etiology). A, August 3. Note the marked elevation of the RST segment in leads I and II and the depressed RST segment in leads IV and V, with slight elevation in lead VI. B, August 17. The patient was considerably improved. The T wave is upright in leads I and II and of somewhat peculiar shape, with no deviation of the RST segment.

I and II, without striking alteration of the RST interval except moderate coving when the T wave was definitely inverted. When healing occurred this type of T wave tended to become flat, and in a few cases we were able to see it finally become normally upright (fig 6B). While an inverted T wave indicates severe derangement of the myocardium, it is not particularly significant of pericarditis unless accompanied with deviation of the RST segment. Cases of this type were of interest to us because an inverted T wave alone without significant deviation of the RST segment was the usual electrocardiographic

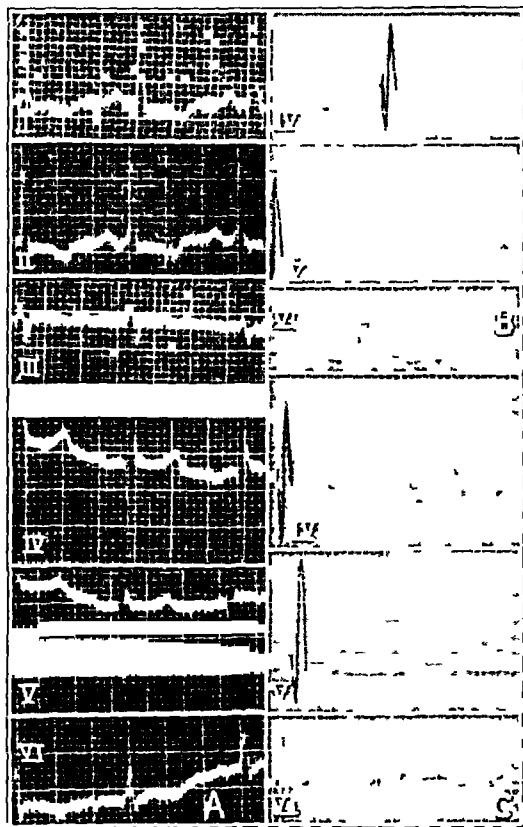


Fig 4—Tuberculous pericarditis, June 18, 1936. These electrocardiograms illustrate the presence of a depression in the RST segment in the precordial lead over the area of friction when none was observed in indirect leads. *A*, leads I to VI, with the anterior electrode placed over the apex; *B*, with the anterior electrode placed over the area of friction, over the third interspace to the left of the sternum (note the depression of the RST segment in leads IV and V); *C*, with the anterior electrode placed over the area of friction, over the xiphoid area (note the depression of the RST segment in leads IV and V, see also lead IV in figure 3C).

finding in cases of tuberculous pericarditis, whereas deviation of the RST segment was the conspicuous change associated with the more rapidly developing virulent form of pericarditis. This will be discussed further in connection with the causes of these changes.

Comment on Electrocardiographic Changes—We have suggested that certain electrocardiographic changes in cases of acute pericarditis may have diagnostic significance. We believe this may be the case when the electrocardiogram conforms strictly to a certain pattern chiefly determined by deviations of the RST segment of direct and indirect leads. However, it is to be recognized that the diagnostic importance of the electrocardiogram is definitely limited by several facts: 1. Striking deviations in the RST segment occur mainly in association with the virulent, rapidly developing types; they are infrequently associated with tuberculous pericarditis. 2. Deviation in the RST segment is always transient, it frequently is of brief duration. 3. The deviation in the RST segment may be slight, not present or not char-

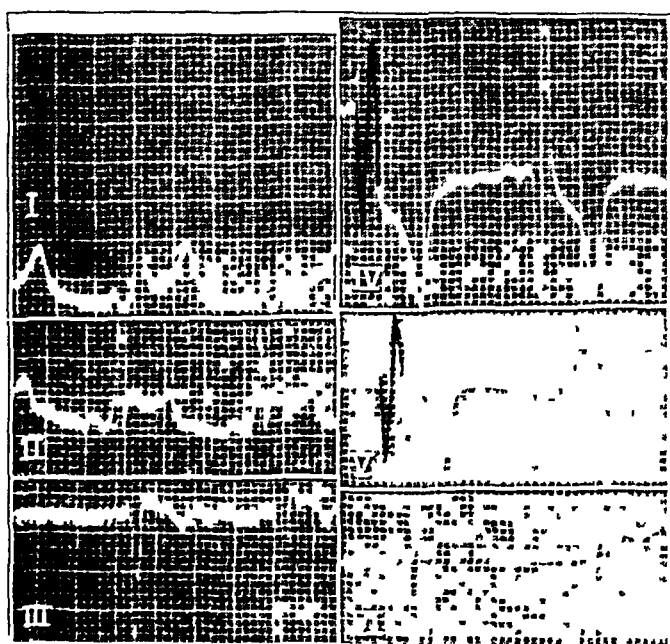


Figure 5—A clinical diagnosis of uremic pericarditis was made for this patient aged 45. Postmortem examination revealed fibrinous pericarditis, with no fluid in the pericardial sac. Microscopic examination revealed a severe grade of hyaline degeneration and hydropic vacuolation of the epicardial portion of the myocardium (fig 9). Note the elevation of the RST segment in leads I to III, even though left axis deviation is present. Note the slight depression of the RST segment in lead IV, with none in lead V, and the elevation in lead VI.

acteristic in sufficient leads to be any more than suggestive. 4. In a considerable number of cases the changes, although definite and indicative of cardiac derangement, are not specific of pericarditis (a flat or inverted T wave in lead I in twelve of twenty cases of tuberculous pericarditis). 5. In a certain number of cases no changes are found (twelve in our series of fifty-seven cases).

These limitations make the diagnosis of acute pericarditis, therefore, still in the main a clinical problem. However, in our opinion the

electrocardiogram, like the roentgenogram, is to be accorded some place in the study of acute pericardial disease, for in our experience it may yield a combination of changes that, so far as we are aware, are not produced by other forms of cardiac disease. How frequently this characteristic electrocardiogram develops is problematic. In our experience it was associated with all forms of acute pericarditis, being noted in twenty-two of forty-seven cases of nontuberculous pericarditis and in two of twenty cases of the tuberculous variety. We have been able to apply these facts advantageously in a few cases, we have

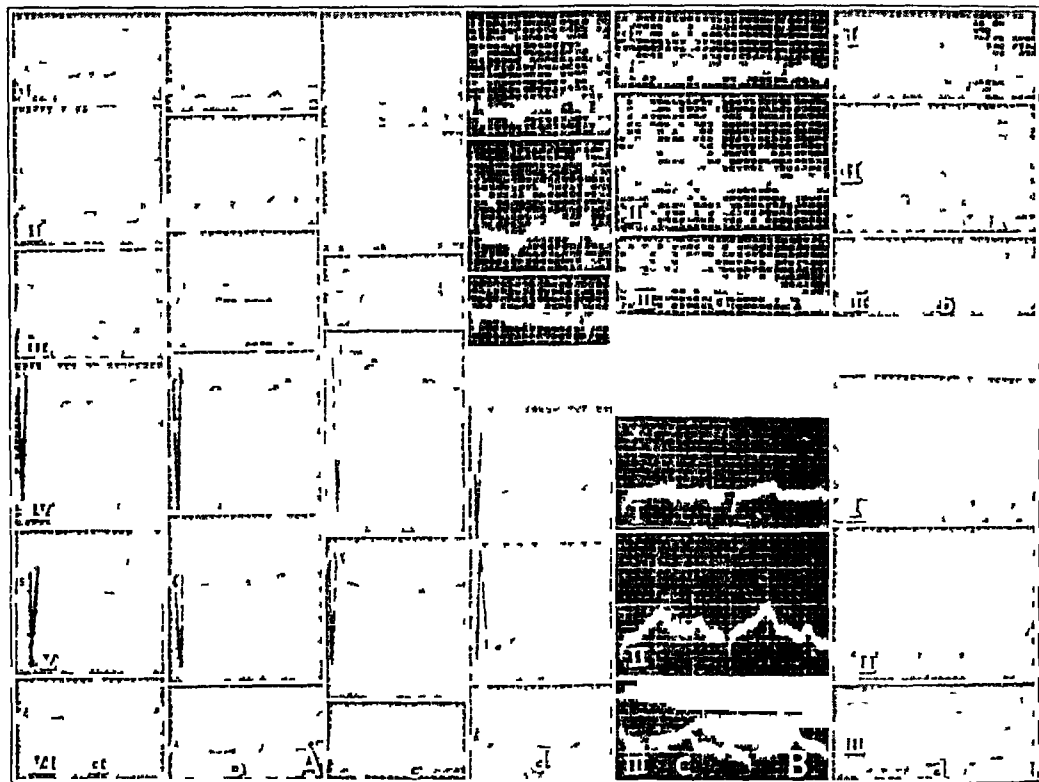


Fig 6—*A*, the clinical diagnosis was tuberculous pericarditis, 350 cc of bloody fluid was obtained on tapping. The patient improved and was discharged in fair condition after a two months' stay in the hospital. *a*, June 18, 1935. The T wave is upright but of low amplitude in leads I and II, aside from a diphasic slightly upright T_6 wave, the precordial leads are within normal limits. *b*, June 21. T_1 is slightly inverted, T_2 is upright, as are also T_4 and T_6 . *c*, June 25. T_1 and T_2 are inverted, T_4 and T_6 upright. *d*, July 18. T_1 and T_2 now are deeply inverted, T_4 and T_6 are upright. *B*, tuberculous pericarditis was the clinical diagnosis for a Negro aged 12. The electrocardiograms show a return to normal as the inflammatory process healed. *a*, March 21, 1936. The T wave is inverted in lead I, the T wave is upright but of low amplitude in lead II. *b*, April 2. T_1 and T_2 are now definitely inverted. *c*, June 17. T_1 is upright but of diminished amplitude, T_2 upright. *d*, November 30. T_1 and T_2 are upright. Examination on November 31 revealed cardiac enlargement, with some diminution in the amplitude of the pulsations but no subjective cardiac complaints.

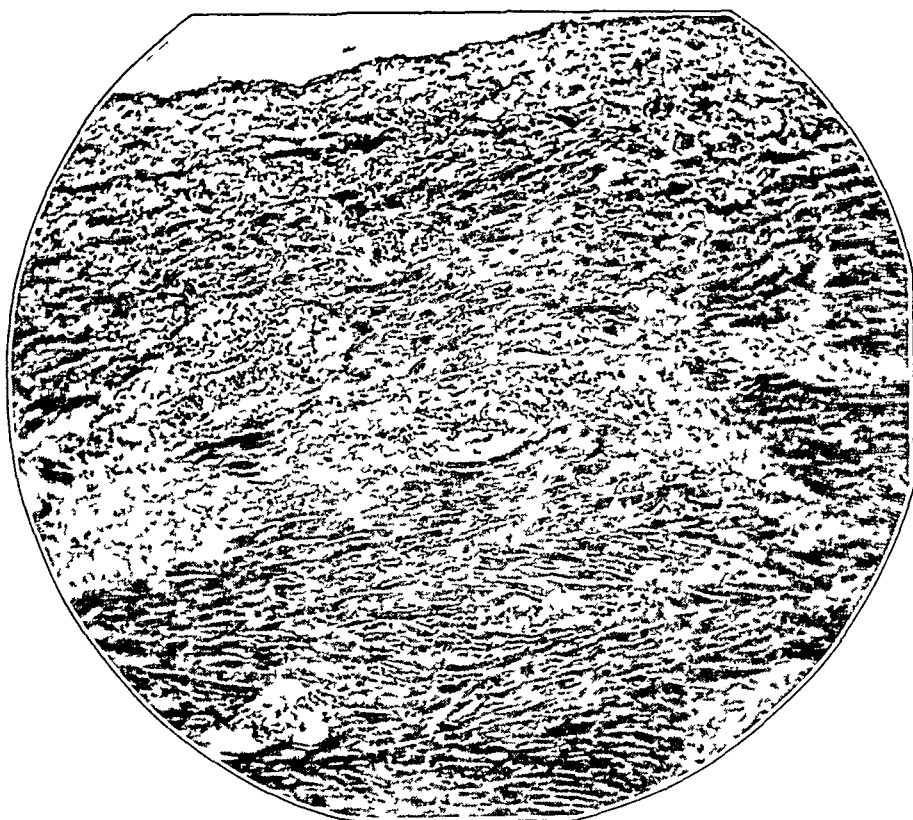


Fig 7—An epicardial portion of the myocardium ($\times 48$) of a patient with pneumococcic pericarditis (electrocardiogram, figure 1) showing the myocardial involvement produced by the pericarditis. Note the severe myocardial degeneration and the leukocytic infiltration extending from the pericardium into the muscle structure.

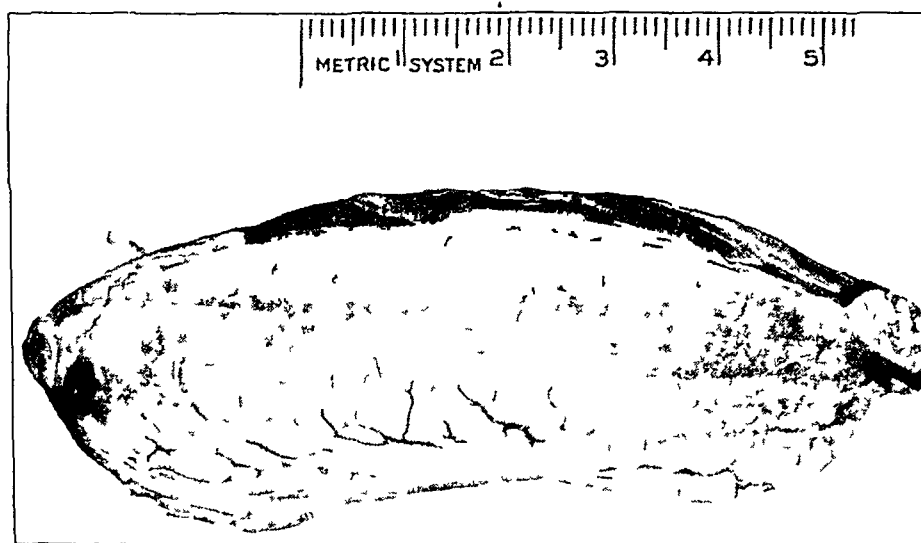


Fig 8—Uremic pericarditis (electrocardiogram, figure 5). In this portion of the muscle of the left ventricle note the numerous areas of pale grayish streaks, concentrated chiefly in the subepicardial zone, where they are extensive.

been led by the findings to recognize in five instances acute pericardial disease, subsequently proved, before clinical study led to its being suspected

CAUSES OF ELECTROCARDIOGRAPHIC CHANGES IN CASES OF PERICARDITIS

The two factors that appear to be the most logical and likely causes of the abnormality of the electrocardiogram in cases of pericarditis are

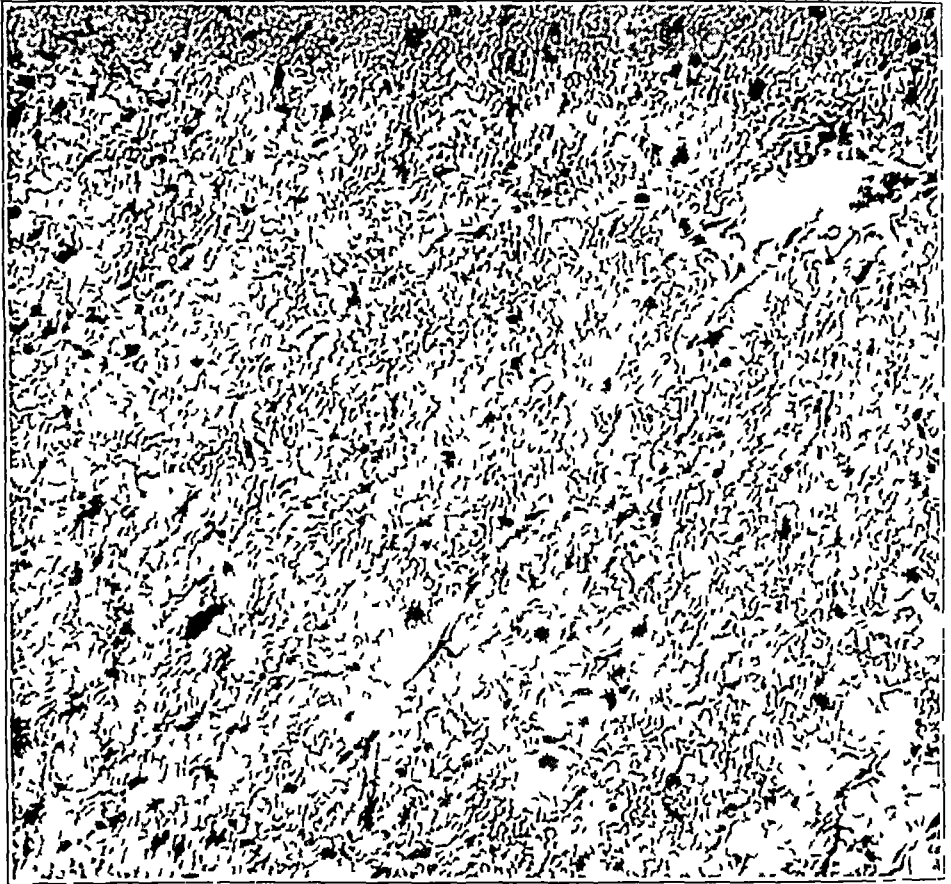


Fig 9—Magnification ($\times 230$) of a section of the muscle depicted in figure 8, showing an area of hyaline degeneration, dissolution of the sarcoplasm and extensive hydropic vacuolation

(1) modification of the coronary circulation by increased intrapericardial pressure and (2) direct involvement of the cardiac muscle

Cardiac Tamponade—Katz, Feil and Scott,⁵ by introducing fluid into the pericardial sac of dogs, produced electrocardiographic changes in the limb leads greatly resembling those which we have been dis-

⁵ Katz, L N , Feil, H , and Scott, R W Electrocardiogram in Pericardial Effusion Experimental, Am Heart J 5 77, 1929

cussing There is therefore little reason to doubt that a large effusion can raise the intrapericardial pressure above the intra-auricular pressure sufficiently to decrease auricular and ventricular filling and thus lower the systemic pressure to the point of impairing the coronary circulation

We judge that derangement of the blood supply secondary to the tamponading effect on the heart of increased intrapericardial pressure is the mechanism most widely accepted as the cause of the abnormality of the electrocardiogram in cases of pericarditis So far as deviations of the RST segment are concerned, a study of our material indicates that these changes, which, in degree at least, so strikingly resemble the monophasic curves produced by acute coronary occlusion, can rarely be attributed to such a mechanism In only three of the twenty-four cases in which the RST deviation was marked and conformed to a certain pattern, which we have described, was the amount of fluid sufficient to suggest this explanation In two cases the pericardium contained a large quantity of blood, resulting respectively from a stab wound and a ruptured dissecting aneurysm, in the third case a pneumococcal infection produced a large effusion In eleven of the remaining twenty-one cases the absence of much fluid was confirmed by necropsy, which revealed plastic pericarditis, either with no fluid or with a small amount which was insufficient to exert any effective pressure In nine of the ten remaining cases in which autopsy was not performed, clinical evidence of any effective effusion was lacking, in the tenth case (pneumococcal pericarditis), we consider that the effusion was not responsible, since the deviation in the RST segment persisted after the pericardium had been opened and drained Considering the matter from a different point of view, in seven cases of tuberculous pericarditis with massive effusion no deviation was observed in the RST segment, though the T wave was flattened or inverted

We cannot draw such definite conclusions concerning the relation of cardiac tamponade to a flattened or inverted T wave without deviation in the RST segment This type of tracing was encountered mainly in our twenty cases of tuberculous pericarditis, and in most of these cases there was accompanying effusion We are doubtful, however, that the latter produced the change, since in several cases inversion of the T wave was observed to persist for a considerable period after most of the fluid had been removed or had spontaneously disappeared

Since cardiac tamponade is not a satisfactory explanation of the electrocardiographic changes, we prefer to consider the role of direct muscular injury as a cause of the changes in the RST segment and T wave in cases of acute pericarditis

Myocardial Injury in Cases of Acute Pericarditis—Although pathologists have appreciated for a long time that a narrow zone of subendocardial muscle may be severely damaged in cases of acute peri-

cardial disease, this fact has not been widely applied as an explanation of the electrocardiographic findings associated with acute pericarditis. Stengel and Fox⁶ stated that the muscle is usually involved, Vaquez,⁷ that it often is, and Karsner,⁸ that it sometimes is affected in cases of pericarditis. Vaquez⁷ placed importance on the muscular changes in cases of pericarditis and attributed "the heart failure sometimes seen in pericarditis to this muscle change." Fowler, Rathe and Smith,⁹ in studying experimental pericarditis in dogs, obtained evidence histologically of inflammation, fragmentation and vacuolation involving the superficial muscle tissue. They attributed to this myocardial involvement the inversion of the T wave encountered and were, so far as we are aware, the first to relate the altered electrocardiogram associated with pericarditis to direct muscular injury. Barnes¹⁰ accepted the conclusions just referred to and, as we have stated, attributed certain unusual electrocardiographic findings that are typical in cases of human coronary occlusion associated with pericarditis to direct myocardial change secondary to the pericarditis. He presented, however, no histologic evidence of myocardial change.

Since other suggested explanations seemed to us to be inadequate, the observations we have just cited, which indicate that the electrocardiographic changes in cases of acute pericarditis are the result of accompanying injury, have appealed to us as suggestive. We have attempted to secure additional information bearing on this relation by studying nineteen cases histologically and attempting to determine the extent to which electrocardiographic and histologic changes can be correlated. The histologic changes are recorded in table 2.

Speaking generally, there were striking myocardial changes in a narrow subendocardial zone of muscle over a considerable extent of the ventricular surface in the cases of rapidly developing virulent types of pericarditis, which included the pneumococcal, rheumatic and uremic varieties. In the tuberculous form, which is slower and more insidious in development, generally either there was no demonstrable myocardial involvement, or slight involvement was seen in only occasional focal

6 Stengel, A., and Fox, H. *A Text-Book of Pathology*, Philadelphia, W. B. Saunders Company, 1915.

7 Vaquez, H. *Diseases of the Heart*, translated by G. B. Laidlow, Philadelphia, W. B. Saunders Company, 1924.

8 Karsner, H. T. *Human Pathology*, Philadelphia, J. B. Lippincott Company, 1926.

9 Fowler, W. M., Rathe, H. W., and Smith, F. M. *Electrocardiographic Changes Following Ligation of the Small Branches of the Coronary Arteries*, *Am Heart J* 8:370, 1933.

10 Barnes, A. R. *Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis*, *Am Heart J* 8:734, 1934.

zones, most of the subendocardial muscle being unaffected. The one case which was an exception to this general statement, in that most of the myocardium was destroyed by tuberculous infiltration, will be referred to subsequently.

TABLE 2—*Histologic Observations in Nineteen Cases of Pericarditis*

Case No	Type of Pericarditis	Changes in T Wave	Days Before Death	Essential Histologic Data for Myocardium
1	Pneumococcic	RST deviation	1	Severe degenerative changes in muscle, cloudy swelling, fragmentation, most marked in subepicardial zone, cellular infiltration into subepicardial portion of myocardium
2	Pneumococcic	RST deviation	1	Same as in case 1, degenerative changes and cellular infiltration marked in subepicardial zone
3	Pneumococcic	RST deviations	2	Same as in case 7
4	Pneumococcic	RST deviation, later, flat T ₁ , inverted T ₂	1	Diffuse severe myocardial degeneration, no predilection to subepicardial zone, no cellular infiltration
5	Pneumococcic	RST deviation later, inverted T ₁	2	Vacuolar and fatty degeneration, cloudy swelling, especially marked in subepicardial zone
6	Staphylococcic	RST deviation	3	Degenerative changes in myocardium, cellular infiltration in subepicardial zone
7	Uremic	RST deviation	1	Hyaline degeneration, dissolution of sarcoplasm and hydropic vacuolation, particularly marked in subepicardial zone (fig. 9)
8	Uremic	RST deviation	1	Same as in case 7, but not so marked
9	Uremic	RST deviation	1	Change in muscle as in case 7, slight in degree and especially confined to subepicardial zone
10	Uremic	Inverted T ₁	1	Cloudy swelling (slight)
11	Neoplastic	Inverted T ₁	1	Extensive carcinomatous infiltration into myocardium, degenerative changes in cardiac muscle
12	Pneumatic	RST originally deviated, inverted T ₁	1	Diffuse degeneration, no predilection to subepicardial zone
13	Unknown	RST deviated in precordial leads only	3	Diffuse degenerative changes throughout muscle, dissolution of sarcoplasm, cloudy swelling, vacuolation, most marked in subepicardial zone
14	Tuberculous	Inverted T ₁	28	Extensive infiltration of caseous process 1½ to 2 inches (3.8 to 5 cm) in thickness into myocardium, resulting in destruction of one half to two thirds of ventricular myocardium, cellular infiltration in outer portion of muscle
15	Tuberculous	Inverted T ₁	4	Slight infiltration into myocardium (small area)
16	Tuberculous	Inverted T ₁	3	Slight cloudy swelling
17	Tuberculous	Flat T ₁ , inverted T ₂	7	No definite change
18	Tuberculous	Inverted T ₁	2	No definite change
19	Tuberculous	Inverted T ₁	3	No definite change

In attempting to discover the relation between these myocardial changes and the accompanying abnormal electrocardiograms, we wish again to consider separately deviation of the RST segment and inversion of the T wave alone.

Only when there was demonstrable myocardial damage was deviation of the RST segment noted. In all five cases of uremic and pneumococcic pericarditis in which this change was present at death there was extensive involvement of the subepicardial zone of muscle. In three additional cases of pneumococcic and one of rheumatic pericarditis, all associated with extensive myocardial change, deviation of the RST segment was originally shown, though there was only an inverted T wave at the time of death some months later. On the other hand, in five of our cases of tuberculous pericarditis and one case of uremic pericarditis in which necropsy was performed and in which no deviation of the RST segment was noted, there was little or no recognizable histologic evidence of myocardial involvement. In still another case of uremic pericarditis in which there was no deviation in the RST segment we considered the myocardium to be practically normal histologically, the only change noted being slight swelling of an occasional muscle fiber.

This is the only direct evidence that we can present which bears on the question under discussion. We regard it as furnishing a fair correlation between the electrocardiographic changes and the myocardial changes and interpret it as supporting the view that the striking deviation of the RST segment associated with certain forms of acute pericarditis are the result of myocardial change that is gross enough to be demonstrable histologically. However, some indirect evidence to support this view is furnished by the similarity in the electrocardiographic behavior noted in cases of acute coronary occlusion and acute pericarditis.

Two facts concerning deviation of the RST segment in cases of acute coronary occlusion are well established. 1. Deviation of the RST segment occurs only after gross myocardial destruction, it is produced however, by injured or dying as opposed to dead muscle. With death of the muscle this deviation disappears and gives way to an inverted T wave, for this reason the change is transient and of relatively brief duration. 2. Myocardial death that is slowly produced by gradual as opposed to sudden closure of a coronary artery does not produce striking monophasic curves, though it may cause inversion of the T wave.

The behavior which we have observed in cases of pericarditis is certainly similar. We have seen deviation of the RST segment only when myocardial damage has been demonstrable post mortem (table 2). This change, as we have shown, is transient and is present only during the early stages of myocardial injury, this suggests, as is observed in cases of acute coronary occlusion, that it is the result of injured and dying rather than dead tissue. This is also suggested by the fact that deviation of the RST segment in our experience, develops chiefly in association with the forms of pericarditis that develop rapidly and malignantly; it is largely absent in cases of the insidious and slowly progressive tuberculous variety of pericarditis. Furthermore, the absence of deviation of

the RST segment in a single case of tuberculous pericarditis in which there was gross destruction of a large portion of the ventricular muscle suggests that when the myocardial injury takes place gradually and insidiously, only inversion of the T wave without deviation results, just as it does with gradual closure of a coronary artery.

Our cases in which a histologic study was made form too small a series on which to base any final conclusions. The evidence furnished, however, as far as it goes, seems to lend definite support to the view that the deviation of the RST segment which is the distinctive electrocardiographic change associated with acute pericarditis, like the similar change associated with acute coronary occlusion, is a result of acute myocardial injury produced by the inflammatory process of acute pericarditis.

So far we have chiefly discussed deviation of the RST segment and have said little concerning the cause of flattening or inversion of the T wave. Since definite alteration of the T wave is an indication of definite myocardial derangement, this abnormal finding must have some definite cause.

With few exceptions, in the cases of acute pericarditis in which there was an initial deviation of the RST segment the T wave became inverted as healing of the pericardial process occurred. The T wave in many instances changed to an upright configuration. Correlation of the electrocardiographic changes with the clinical progress of the pericarditis and the necropsy data suggest that the occurrence of deviation of the RST segment was associated with severe changes in the subepicardial portion of the myocardium, either inflammatory or degenerative. Inversion of the T wave was probably associated with the subacute or subchronic stage and occurred when the pericardial process was healing and the general toxemia was less marked. With tuberculous pericarditis, which, as already stated, occurred in a much less virulent form than the nontuberculous variety, inversion of the T wave, rather than deviation of the RST segment, was the characteristic electrocardiographic change.

In one of the six cases¹¹ of tuberculous pericarditis in which necropsy was performed gross myocardial damage was present, in the remainder the myocardial damage was slight, in some of these cases we could demonstrate an occasional area in which the inflammatory process had apparently penetrated only superficially into small areas of the myocardium. Aside from these changes little histologic evidence of myocardial damage was seen. The added factor of pericardial effusion in producing changes in the T wave in three of the six cases is to be considered, however, we have observed these changes in the absence of

¹¹ In one case, after pericardiectomy, there were inflammatory changes in the subepicardial portion of the myocardium which were probably due to secondary infection. This case is omitted from consideration here.

effusion It should be stated here that it is not unusual to fail to observe demonstrable histologic and other changes to account for the presence of an abnormal T wave Our findings lead us to attribute the alteration in the T wave in cases of tuberculous pericarditis to the effect of inflammatory changes of the pericardium which produce functional derangement of the underlying muscle and general toxemia and in some instances cause the formation of pericardial fluid

DIAGNOSTIC IMPORTANCE OF ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PERICARDITIS AND CORONARY OCCLUSION

Not only are the electrocardiographic findings associated with pericarditis and coronary occlusion similar, but the clinical pictures also may be similar However, as we have indicated, we believe that in cases of pericarditis unassociated with coronary occlusion there are certain distinct features that enable one to differentiate between these two conditions When the electrocardiographic findings are typical (demonstrated in two cases of our series and consisting of elevation of the RST segment in the three limb leads, its depression in leads IV and V and its elevation in lead VI, with preservation of the initial downward deflection) the differential diagnosis is as a rule comparatively easy, for pericarditis is strongly suggested We are not acquainted at present with any condition other than pericarditis that can yield a similar combination of electrocardiographic findings, and we have noted no instance of coronary occlusion that has exactly produced them In all our cases in which necropsy was performed and in which these findings were noted (21 cases) pericarditis alone was present

The common types of coronary occlusion, namely the T_1 and T types, produce changes in the limb and precordial leads which are easily differentiated from those typical of cases of pericarditis The only cases of coronary occlusion in which the electrocardiographic changes may be confused with those seen in cases of pericarditis are the rather rare ones in which the infarction involves both the anterior and the posterior surface of the left ventricle¹² While this type of infarction produces elevation of the RST segment in the three limb leads the picture differs definitely from that produced by pericarditis in that first, the elevation of the RST segment in lead III is slight, while in lead II it is approximately the algebraic sum of the elevations in leads I and III and lead V shows less deviation of this segment than does lead IV, secondly, a Q wave is usually present in leads II and III (neither in the cases in our series nor in the cases reported with which we are acquainted was there

12 Wolferth C C, Wood, F C, and Bellet, S Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch Int Med 56 77 (July) 1935

a Q wave in the electrocardiogram which could be definitely attributed to pericarditis), and, thirdly, the major points of differences are seen in the chest leads. Most important is the fact that in all cases within our experience in which there was both anterior and posterior infarction there was no initial downward deflection in leads IV and V, which is characteristic of infarction of the anterior portion of the left ventricle. In cases of pericarditis the original configuration of the QRS complex is not changed, in spite of striking alteration of the RST interval in both limb and chest leads.

In cases of pericarditis in which elevation of the RST segment is present in leads I and II only, and not in lead III, the electrocardiogram goes far toward establishing pericarditis rather than coronary occlusion as the cause—when the findings of the precordial lead are typical. If extensive pericarditis is present with coronary occlusion the differential diagnosis may of course be extremely difficult—if not impossible. The presence of previous myocardial infarction, an abnormal position of the heart or the effect of digitalis add to the difficulty of the diagnosis. In this connection the importance of serial electrocardiograms is emphasized, since the diagnostic implications, which may have no differential value if based on only one electrocardiogram, may become definite when successive electrocardiograms are available for examination.

SUMMARY AND CONCLUSIONS

The electrocardiographic findings in fifty-seven cases of acute pericarditis of different etiologic types are presented and discussed.

On the basis of these observations it is concluded that in a large majority of cases (80 per cent in this series) electrocardiographic changes are associated with pericarditis. In twenty-one cases (more than 37 per cent) the alteration in the RST segment conformed to a pattern which we regard as fairly characteristic, namely, elevation of the RST segment in the three limb leads, depression of the interval in leads IV and V and elevation of the interval in lead VI, with preservation of the initial downward deflection. In the remainder the inversion of the T wave and minor changes in the RST segment, which are considered important, were noted. In the main, the deviation in the RST segment was observed in association with the more virulent forms of pericarditis, e. g., pneumococcal, uremic and rheumatic, the alteration in the T wave was the outstanding change present in cases of tuberculous pericarditis.

The deviation in the RST segment and the change in the T wave are transient, for this reason it is important to obtain electrocardiographic records at frequent intervals.

The use of precordial leads as an important aid in the diagnosis is herein recorded, additional information was sometimes obtained by placing the anterior electrode over the area of friction.

The basing of a differential diagnosis on the electrocardiographic findings in cases of pericarditis and coronary occlusion is discussed

Histologic studies of the cardiac muscle were made in nineteen of the cases of our series. From these observations, together with other factors mentioned, it is concluded that invasion of the subpericardial portion of the myocardium by pericarditis is chiefly responsible for the deviation observed in the RST segment.

Frequently, in spite of the presence of frank pericarditis, no electrocardiographic changes are observed. This is probably due to the absence of myocardial involvement or to the presence of an extremely slight grade of involvement.

The chiefs of the various medical, surgical and tuberculous services gave us permission to study and report these cases.

IRON RETENTION IN PERNICIOUS ANEMIA, LEAD POISONING AND MYXEDEMA

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AND

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Many data have been accumulated on the iron requirements of normal and of pathologic subjects,¹ as well as on the amount of iron which is retained and utilized by patients with anemia of various types.² We have shown that patients with hypochromic anemia retain a large amount of iron but utilize only a relatively small percentage of that retained^{2a} and that the absence of hydrochloric acid in the gastric juice interferes with the retention of dietary iron but has no effect when large doses of medicinal iron are administered.³ We have also shown that the degree of anemia which is present has no appreciable effect on the amount of iron retained.³ The effect of copper and of a liver fraction given in combination with the iron has also been studied,⁴ as well as the results obtained with variable amounts of iron.⁵ We wish to present in this communication the results of iron balance studies of patients with pernicious anemia, chronic lead poisoning and myxedema

Supported in part by a grant from Eli Lilly & Co

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1 The Iron Requirement of Man, editorial, *J A M A* **105** 1917 (Dec 7) 1935 Farrar, G E, and Goldhamer, S M The Iron Requirement of the Normal Human Adult, *J Nutrition* **10** 241, 1935 Ohlson, M A, and Daum, K A Study of the Iron Metabolism of Normal Women, *ibid* **9** 75, 1935 Barer, A P, and Fowler, W M The Iron Requirements of Adults, to be published

2 (a) Fowler, W M, and Barer, A P Retention and Utilization of Orally Administered Iron, *Arch Int Med* **59** 561 (April) 1937 (b) Brock, J F, and Hunter, D The Fate of Large Doses of Iron Administered by Mouth, *Quart J Med* **6** 5, 1937 (c) Lintzel, W Neuere Ergebnisse der Erforschung des Eisenstoffwechsels, *Ergebn d Physiol* **31** 844, 1931 (d) Reimann, F, Fritsch, F, and Schick K Eisenbilanzversuche bei Gesunden und bei Anämischen, *Ztschr f klin Med* **131** 1, 1936

3 Barer, A P, and Fowler, W M Influence of Gastric Acidity and Degree of Anemia on Iron Retention, *Arch Int Med* **59** 785 (May) 1937

4 Barer, A P, and Fowler, W M The Influence of Copper and a Liver Fraction on Iron Retention, *Arch Int Med* **60** 474 (Sept) 1937

5 Fowler, W M, Barer, A P, and Spielhagen, G F Retention and Utilization of Small Amounts of Orally Administered Iron, *Arch Int Med* **59** 1024 (June) 1937

The important clinical features in each of these cases are given in table 1 and the hematologic findings, gastric acidity and basal metabolic rates in table 2

METHOD

The patients received iron in the form of iron and ammonium citrates in combination with a liver fraction⁶ The amount of iron which they received was determined by analysis of representative samples of this preparation, and the dietary

TABLE 1—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	57	F	Pernicious anemia	Had received liver extract but in inadequate amounts, rather slow response to liver extract
2	38	F	Pernicious anemia	Had received liver extract in inadequate amounts, slow response to liver extract
3	32	M	Lead poisoning	Had worked in battery repair shop breaking up old storage batteries and making new ones
4	54	F	Lead poisoning	Had used one brand of face powder continuously for 38 years analysis revealed that this consisted almost exclusively of lead carbonate
5	59	M	Myxedema	Had received thyroid extract intermittently for several years died of coronary occlusion
6	52	F	Myxedema	Gradually increasing symptoms for 10 years prior to admission to hospital presented all characteristic features
7	69	F	Myxedema	Increasing symptoms for 3 years presented all characteristic features

TABLE 2—*Laboratory Data**

Patient	Hemoglobin, %	Hematocrit Reading, %	Erythrocytes, %	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	62	90	92	0.67	0.97	0.69	0	—
2	82	89	93	0.88	1.08	0.92	0	+24
3	56	74	67	0.83	1.10	0.75	—	—
4	56	68	63	0.88	1.07	0.82	0	—
5	85	95	87	0.97	1.09	0.89	0	—38
6	49	65	58	0.84	1.12	0.75	Normal	—41
7	55	71	65	0.84	1.09	0.77	Normal	—35

* The hemoglobin, hematocrit and erythrocyte values are given in percentage of normal values, as calculated from the tables of Osgood (*A Textbook of Laboratory Diagnosis*, ed 2 Philadelphia, P. Blakiston's Son & Co., 1935, p. 420)

intake of iron was calculated from the tables of Rose.⁷ The procedures were the same as those described in a previous report.²¹ The balance studies were preceded by a three day period of adjustment, during which the patients received the regular balance diets. This was followed by a six day control period, during which they received no medicinal iron. Patients 1, 3 and 5 were studied for only one period and did not receive additional iron, and patient 7 was studied for two six day periods before the administration of iron was begun. The control period for patient

6 The preparation used was Iextron.

7 Rose, Marv S. *Laboratory Handbook for Dietetics*, ed 3, New York: The Macmillan Company, 1929.

TABLE 3—Results of Balance Studies

Patient	Period	Average Daily Nitrogen Balance, Gm			Average Daily Phosphorus Balance, Gm			Average Daily Iron Balance, Mg			Erythrocytes, Millions	Hemoglobin, Gm	Hematocrit Reading, %
		Intake	Excretion	Balance	Intake	Excretion	Balance	Intake	Excretion	Balance			
1	1	13.484	11.917	+1.567	1.668	1.603	+0.065	19.98	23.04	— 3.06	4.665	8.905	38.5
2	1	13.484	15.620	—2.136	1.608	1.787	—0.119	19.98	33.82	— 13.84	4.470	11.715	40.0
	2	14.492	16.376	—2.087	1.701	2.231	—0.530	283.98	187.21	+ 96.77	4.510	12.140	40.0
	3	14.492	15.620	—1.128	1.701	1.901	—0.200	283.98	210.55	+ 73.43	4.460	12.200	41.5
3	1	10.114	8.613	+1.501	1.499	0.979	+0.510	12.75	7.98	+ 5.77	3.343	8.210	30.0
4	1	9.843	7.934	+2.509	1.442	1.090	+0.352	11.49	9.22	+ 2.27	3.150	8.034	29.0
	2	11.346	8.863	+2.483	1.505	1.219	+0.286	263.78	110.51	+153.21	3.040	8.420	28.0
	3	10.449	8.812	+1.667	1.440	1.247	+0.193	269.55	115.96	+153.59	3.330	8.830	30.0
	4*	11.321	9.330	+1.791	1.568	1.263	+0.245	269.83	122.04	— 52.21	3.683	10.320	32.5
	5	11.126	10.124	+0.702	1.510	1.311	+0.199	269.81	240.25	+ 19.00	3.550	10.090	32.0
5	1	10.667	7.739	+2.928	1.478	0.933	+0.545	12.19	4.53	+ 7.66	4.360	12.488	39.0
6	1	9.795	14.121	—4.326	1.414	1.745	—0.101	11.91	5.81	+ 6.10	2.910	7.058	28.0
	2	10.789	11.940	—3.151	1.472	1.067	+0.405	275.69	160.54	+115.15	3.200	7.077	29.0
	3	11.513	12.276	—0.763	1.520	1.100	+0.420	276.38	190.65	+ 85.07	3.470	7.058	28.5
	4	11.716	12.161	—0.455	1.534	1.142	+0.392	276.53	187.29	+ 89.23	3.470	7.115	29.0
7	1	9.811	7.968	+1.843	1.451	1.177	+0.277	11.78	10.72	+ 1.06	3.283	7.945	30.5
	2	9.401	11.034	—1.630	1.417	1.426	—0.009	11.62	11.64	— 0.02	3.110	8.378	28.5
	3	10.051	12.305	—2.254	1.377	1.627	—0.250	262.96	160.46	+102.50	2.880	8.173	29.0
	4	10.098	16.750	—6.652	1.373	1.623	—0.250	262.77	180.49	+ 82.28	3.180	8.267	31.0
	5	10.549	12.558	—2.009	1.429	1.378	+0.051	263.43	227.26	+ 36.18	3.160	8.868	30.0

* Forty five days between periods 3 and 4. Twelve capsules per day of a combination of iron and liver extract were taken during that time.

2 was complicated by menstruation, so that the markedly negative iron balance is partially explained on this basis. All balance periods were of six days' duration, and carmine was used to mark the stools at the beginning and at the end of each period. The excreta were carefully collected and stored in glass or porcelain-lined containers. Nitrogen was determined by the Kjeldahl method, phosphorus by the method of Fiske and Subbarow⁸ and iron by the method of Reis and Chakmakjian.⁹

The complete results of the balance studies are given in table 3, and a summary of the data on iron retention is given in table 4.

RESULTS

Pernicious Anemia—Various iron balance studies have been made on patients with pernicious anemia. Queckenstedt¹⁰ has stated that there is no correlation between the fall in the blood count and the rate of urinary excretion of iron. Riecker¹¹ has shown that the iron content of the serum is higher during a relapse in pernicious anemia but returns

TABLE 4—Average Daily Iron Balance by Periods

Patient	Iron Balance, Mg					Total Iron Retained,* Mg	Percentage of Iron Retained
	Control Period	Period 1	Period 2	Period 3	Period 4		
1	— 3.06					—	
2	—13.84	+ 96.77	+ 73.43			1,021.20	29
3	+ 5.37					—	
4	+ 2.27	+153.24	+153.39	—52.21	+19.90	1,645.92	25
5	+ 7.66					—	
6	+ 6.10	+115.15	+ 85.07	+89.23		1,736.70	4
7	+ 1.06	— 0.02†	+102.50	+82.28	+ 16.18	1,255.76	21

* Exclusive of control periods.

† No medicinal iron was given.

to normal during a remission and that a remission is accompanied with an increase in the excretion of iron. Gibson and Howard¹² have demonstrated that a favorable iron balance may be readily established in patients with pernicious anemia when a diet rich in iron is given and that iron retention may occur in the presence of a negative nitrogen balance.

Patient 1 of our series was in a negative iron balance of 3.06 mg per day while receiving a diet containing 19.98 mg of iron. She was in positive nitrogen balance. Patient 2 was in a markedly negative

8 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**: 375, 1925.

9 Reis, F., and Chakmakjian, H. H. Colorimetric Method for Quantitative Determination of Iron in Blood in the Form of Dispersed Prussian Blue, *J. Biol. Chem.* **92**: 59, 1931.

10 Queckenstedt, H. Untersuchungen über den Eisenstoffwechsel bei der perniziösen Anämie, mit Bemerkungen über den Eisenstoffwechsel überhaupt, *Ztschr. f. klin. Med.* **79**: 49, 1914.

11 Riecker, H. H. Iron Metabolism in Pernicious and Secondary Anemia, *Arch. Int. Med.* **46**: 458 (Sept.) 1930.

12 Gibson, R. B., and Howard, C. P. Metabolic Studies in Pernicious Anemia, *Arch. Int. Med.* **32**: 1 (July) 1923.

iron balance during the control period although this was partially accounted for by the menstrual loss of blood. Both of these patients were in a partial remission induced by liver extract but improvement had ceased in spite of the continued administration of a potent liver extract. The hemoglobin value for both increased to normal with the subsequent administration of iron and liver extract. With the administration of iron and ammonium citrates in combination with a liver fraction it was found that patient 2 retained a large amount of iron (tables 3 and 4). During the first period of administration of iron she received 283.98 mg per day and retained 96.77 mg. During the second period with a similar intake she retained 73.43 mg per day. For the entire period of administration of iron she retained 29 per cent of the amount given. When the same preparation of iron with a liver fraction was administered in similar amounts to a group of patients with hypochromic anemia the retention varied from 13.2 to 31.1 per cent with an average of 20.4 per cent⁴. Although the hemoglobin value for patient 2 increased only 0.485 Gm per hundred cubic centimeters of blood in the twelve days of the balance study there was a further increase after the balance study was completed whereas the hemoglobin value had previously been nearly stationary with liver extract alone.

Lead Poisoning—Two patients (3 and 4) with chronic lead poisoning were studied in a similar manner. Patient 3 was under observation for only one six day period with no medicinal iron. During this period he retained 5.37 mg of iron per day from the diet alone. Patient 4 retained 2.27 mg from the dietary iron and was studied for four additional balance periods while receiving medicinal iron. She was given a combination of iron and ammonium citrates with a liver fraction and received from 263.78 to 269.83 mg of iron per day. During the first two periods of administration of iron 153.24 and 153.39 mg respectively was retained; during the third period there was a negative balance of 52.21 mg per day and in the fourth period only 19.9 mg was retained per day. For all four periods 25 per cent of the iron which was administered was retained, an amount which is but slightly higher than the average of 20.4 per cent for the patients with hypochromic anemia previously reported. During the first twelve days the hemoglobin value increased 0.066 Gm per day but during the last twelve days no increase occurred. There was an interval of forty-five days between these periods during which the patient received the liver and iron continuously.

Hypothyroidism—Three patients with typical myxedema were similarly studied. Patient 5 was in a positive iron balance of 7.66 mg per day with a dietary intake of 12.19 mg in spite of the fact that he had achlorhydria. Patient 6 with normal gastric acidity was in a posi-

tive balance of 61 mg from a diet containing 1191 mg of iron. With the administration of iron and ammonium citrates and a liver fraction, large amounts of iron were retained, and during the three periods she retained 34 per cent of the iron which was administered. During this time there was but a slight increase in the hemoglobin value—0.357 Gm in eighteen days. Thyroid extract was being administered during this time. For patient 7 there were two control periods in which the iron balances were +1.06 and -0.02 mg per day, respectively. During the following three periods she retained 27 per cent of the iron administered. The increase in the hemoglobin value during this period was small, amounting to 0.027 Gm per day. This patient was also receiving thyroid.

COMMENT

The results of the iron balance studies of these patients show a retention of iron varying from 25 to 34 per cent. This is slightly, but not significantly, greater than the retention which was obtained with similar amounts of the same preparation when given to a group of patients with hypochromic or iron deficiency anemia⁴. This indicates that the type of anemia does not influence the amount of iron which is retained and is in keeping with the previous report³ showing that the degree of anemia does not influence the retention of iron. The results reported here were obtained for patients with three entirely different types of anemia.

Patients with pernicious anemia retained 29 per cent of the iron, and the hemoglobin value increased at the rate of 0.04 Gm per day. It has been shown that iron is advantageous in certain of these cases, particularly when the hemoglobin value and the erythrocyte count have increased to a certain level and have then remained stationary in spite of continued liver therapy. Such was the case in these two patients with pernicious anemia, and after the balance studies were discontinued the hemoglobin values continued to increase with the administration of the combination of iron and liver extract.

One patient with chronic lead poisoning retained 25 per cent of the iron administered. The hemoglobin response to this amount of iron was not extremely rapid (0.06 Gm per day) but was such that the medication seemed to be advantageous. There was no evidence of a deficiency of iron in these patients, but nevertheless the retention of iron and the hemoglobin response obtained with the combined liver extract and iron justify its use.

There is some dispute as to the proper therapy for the anemia associated with myxedema. Baldrige and Greene¹³ have shown that

13 Baldrige, C. W., and Greene, J. A. Absence of Response of Anemia of Myxedema to Liver Extract, *Proc Soc Exper Biol & Med* **31** 1035, 1934.

there is no response to the administration of liver extract in these patients Lerman and Means¹⁴ have stated the opinion that liver is of value in accelerating or initiating the erythrocyte response in certain cases They showed that thyroid extract alone may cause a slow improvement in the anemia but that the anemia persists in some cases They concluded that iron produced the most rapid improvement Our results from the administration of a combined liver and iron preparation show that 27 and 34 per cent of the iron, respectively, was retained by two patients and that the hemoglobin response amounted to 0.019 and 0.027 Gm, respectively per day Although this is not a particularly rapid response, it is more rapid than that obtained with thyroid extract or liver extract alone Whether or not this combination of liver and iron is more advantageous than iron alone cannot be answered from this experiment However, it has been shown that iron is retained under these circumstances in this type of anemia and that a satisfactory hemoglobin response ensues

SUMMARY

Iron balance studies were made of patients with pernicious anemia, chronic lead poisoning and myxedema Iron and ammonium citrates was administered in combination with a liver fraction, and it produced a retention of from 25 to 34 per cent of the administered iron This is comparable to the amount of iron retained in hypochromic anemia under similar circumstances

¹⁴ Lerman, J, and Means, J. H. Treatment of the Anemia of Myxedema, *Endocrinology* **16** 533, 1932

GRANULOCYTOPOIETIC FRACTION OF YELLOW BONE MARROW

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At the meeting of the American Medical Association in Milwaukee in 1933 Dr C H Watkins, of the Mayo Clinic, announced that a strained preparation of yellow bone marrow had been beneficial in cases of granulocytopenia. After the use of the yellow marrow, monocytosis occurred and was rapidly followed by an increase in the number of polymorphonuclear neutrophils. This reaction occurred generally within twenty-four to forty-eight hours after ingestion of the marrow¹. A report of this work has not yet been published by Dr Watkins.

Shortly after this announcement Dr M J Flipse, of Miami, Fla., successfully used yellow bone marrow for a series of patients suffering from granulocytopenia². This preparation is extremely unpalatable and has the further disadvantage that it must be taken in very large doses (60 to 120 Gm or more daily), in some cases large enough to interfere with normal metabolism. Dr Flipse expressed to Dr F Fenger, of Armour & Co, the need of a potent concentrate of the active principle of yellow bone marrow, and Dr Fenger, in turn, presented the problem to one of us (C M M), who was at the time the Armour Fellow in the Otho S A Sprague Memorial Institute.

* Armour Fellow in the Otho S A Sprague Memorial Institute

From the Otho S A Sprague Memorial Institute and the Department of Pathology, the University of Chicago

This paper contains the essential features of a preliminary report presented to the Medicinal Section of the American Chemical Society at the meeting in Cleveland on Sept 11, 1934. Publication was withheld pending the accumulation of a larger series of clinical data or the development of a reliable method of animal assay which would establish beyond any doubt the activity of our material and lead the way to further chemical purification of the granulocytopoietic substance. We are now publishing our data because of the recent appearance of a paper under an almost identical title by J Zichis (*Granulocytopoietic Fractions of Yellow Bone Marrow*, *J Lab & Clin Med* **22** 231 [Dec] 1936), which will be criticized in the body of this paper. A preliminary report was recently published by us (*Yellow Bone Marrow Extracts in Granulocytopenia*, Preliminary Report, *J A M A* **109** 1965 [Dec 11] 1937).

1 Watkins, C H. Personal communication to the authors

2 Flipse, M J. Preliminary report to the meeting of the Florida State Medical Society, 1934

CHEMICAL PREPARATION

In the preparation of such an active concentrate the first consideration was the undesirability of the large amount of free fat present in yellow bone marrow. There was no reason to believe that either fat or fatty acids were necessary for granulocytopoiesis, and it seemed improbable that any of the less abundant saponifiable constituents (phosphatides, for instance) would be necessary. Accordingly, the first step taken was the removal of the saponifiable fraction.

The beef marrow was subjected to saponification with an excess of alcoholic potassium hydroxide at the refluxing temperature. After dilution of the soap solution with water, the nonsaponifiable fraction was extracted in the usual way (ether, ligroine or, better, ethylene dichloride was used). The solvent was removed in vacuo, and a reddish brown semicrystalline waxy residue remained. The yield varied between 0.1 and 0.2 per cent of the weight of the crude marrow used. This residue was dissolved in a bland oil (peanut, corn or cottonseed) for oral administration in such concentration that each drop (0.05 cc) was equivalent to 2 Gm of strained yellow bone marrow. It has been shown by clinical test that practically all the activity of the original marrow is contained in the nonsaponifiable fraction.

The yellow bone marrow used in this work was from the tibias and femurs of cattle, being obtained in clean condition, free from bone, blood and other extraneous material. Over 250 Kg has been worked up in our laboratory in the following manner:

Saponification Number—A 1 Kg sample of the crude marrow was repeatedly ground until a uniform sample could be obtained. The saponification number was determined by the usual method:

4.4817 Gm required 761.16 mg of potassium hydroxide

5.8172 Gm required 990.73 mg of potassium hydroxide

Average value for saponification number, 170.1

Saponification and Extraction—For lot 2 (Oct. 20, 1933) 4,200 Gm of fresh beef yellow bone marrow was added slowly to a hot solution of 1,250 Gm of commercial potassium hydroxide (92 per cent) in 3,000 cc of alcohol. The material was boiled under a reflux condenser, agitation being accomplished by blowing a stream of nitrogen through the material. When the saponification was complete, in one to two hours, 3,000 cc of water was added, and the resulting clear dark brown solution was allowed to cool to room temperature, then it was extracted with ethylene dichloride as follows. Two liters of the soap solution was shaken with 1 liter of ethylene dichloride, of which about 525 cc went into solution. The rest separated fairly readily and was drawn off. For each of the next four extractions 500 cc of ethylene dichloride was used. These volumes were recovered almost quantitatively. The combined ethylene dichloride extracts were dried over sodium sulfate after being washed with water. The rest of the soap solution was similarly extracted, and the combined extracts were evaporated in vacuo at a bath temperature not exceeding 50°C. The residue was a deep reddish brown oil, which solidified on cooling. The yield, 4 Gm, represented 0.1 per cent of the weight of bone marrow used.

For lot 4, 15 Kg was worked up in the same way and yielded 205 Gm of residue, and for lot 5, 148 Kg was worked up and yielded 206 Gm. Our yields have varied between 0.1 and 0.2 per cent—we have never even approached the figure given by Zichis,³ whose material undoubtedly contains free fat, since the amount of alkali used by him in his first preparation (6 liters of 3 per cent alcoholic potassium hydroxide for 2 Kg of bone marrow) is about half that required for complete saponification of the fats. Our material contains a large amount of cholesterol, in contrast to his, which "gave a negative test for sterols." We have also been able to isolate a small amount of crystalline carotene from our preparation.

EXPERIMENTAL TESTING OF GRANULOCYTOPOIETIC AGENTS

The difficulty of testing our preparations has led us to investigate the possibility of the experimental induction of granulocytopenia in animals. In attempts to determine the etiologic factors of the disease many investigators have also sought to produce the condition in animals. Kracke and Parker⁴ were able to produce neutropenia in only an occasional animal of a large series by intravenous injection of hydroquinone, catechol, aniline, para-aminophenol, quinone and phenol but they were not able to reproduce the clinical picture. Madison and Squier⁵ were able to produce granulocytopenia in only one rabbit of a series to which they administered aminopyrine. Stenn⁶ in this laboratory, gave aminopyrine intravenously over a long period to a series of one hundred and twenty animals (guinea pigs, rabbits and monkeys) without success. He also superimposed treatment with aminopyrine on experimental anemia and on infections in animals but failed to get results. Many workers⁷ have unsuccessfully attempted to produce the condition by inoculation of animals with organisms isolated from patients dying of the disease. Yet a few, for instance, Fried and Dameshek,⁸ have

3 Zichis, J. Granulocytopenic Fractions of Yellow Bone Marrow, *J. Lab & Clin Med* **22** 231 (Dec) 1936.

4 Kracke, R. R., and Parker, F. P. The Etiology of Granulopenia (Agranulocytosis), *J. Lab & Clin Med* **19** 799 (May) 1934.

5 Madison, F. W., and Squier, T. L. The Etiology of Primary Granulocytopenia (Agranulocytic Angina), *J. A. M. A.* **102** 755 (March 10) 1934. Squier, T. L., and Madison, F. W. Primary Granulocytopenia Due to Hypersensitivity to Amidopyrine, *J. Allergy* **6** 9 (Nov) 1934.

6 Stenn, Fred. Etiology of Agranulocytosis, *Arch. Path.* **20** 902 (Dec) 1935, The Etiologic Relationship of Amidopyrine to Agranulocytosis, *J. Lab & Clin Med* **20** 1150 (Aug) 1935.

7 Lovett, B. Agranulocytic Angina, *J. A. M. A.* **83** 498 (Nov 8) 1924. Linthicum, F. H. Experimental Work with the Bacillus Pyocyaneus. Report of a Case of Pyocyanic Stomatitis with Agranulocytic Leucopenia, *Ann. Otol., Rhin. & Laryng.* **36** 1093 (Dec) 1927. Keeney, M. J. Pyocyanic Angina, with Agranulocytosis, *California & West Med* **33** 503 (July) 1930.

8 Fried, B. M., and Dameshek, W. Experimental Agranulocytosis, *Arch. Int. Med.* **49** 94 (Jan) 1932.

reported the induction of primary granulocytopenia in rabbits by intravenous injection of *Salmonella supestifer*. Their data do not indicate a reproduction of the clinical picture, but rather a temporary neutropenia, such as generally follows the injection of killed organisms. Piersol and Steinfield⁹ injected Berkefeld filtrates and supernatant fluids from cultures and called attention to the fact that injections of peptones and a large number of proteins cause temporary leukopenia.

Dennis¹⁰ placed a capsule containing a broth culture of pyogenic bacteria in the abdomen of each of a series of rabbits and obtained nonconclusive results with *Staphylococcus aureus*, *Streptococcus haemolyticus* and *Bacillus proteus*. With a large dose of *Streptococcus viridans* in relation to the size of the animal, he obtained sustained and marked granulocytopenia. Zichis³ used the technic of Dennis and *Staph. aureus* as the organism with a series of forty-six rabbits. Of these, only "seventeen developed granulocytopenia, nine died without showing any change in the leucocytic picture, and twenty recovered without any apparent ill effects." He described no control animals and gave data for only nine of the rabbits used. According to Zichis' own data, four of these rabbits (no. 2, 5, 6 and 9) showed a distinct decrease in the total leukocyte count after a temporary rise while receiving his medication. At most, his results are only indicative, being not at all conclusive. We believe that the Dennis technic as used by Zichis is not at all reliable and that for the present at least it is necessary to use human subjects.

Patients with granulocytopenia are generally so ill that it is hard to deny them anything that may be beneficial, and so they are generally given several medicines simultaneously. It is therefore difficult to determine the efficacy of any one preparation. However, we were able to obtain reports of a few cases in which other medication was discontinued in favor of our concentrate, and the results obtained were convincing. Also, the relatively prompt response to yellow bone marrow concentrate often distinguishes its effect from the possible action of other therapeutic agents.

We tested our material on a series of six normal persons in our laboratory and found no effect on the leukocyte counts. Flipse¹¹ found that only one of five normal persons in his laboratory responded. This person showed an increase to 12,000 leukocytes within twenty-four hours after taking 10 Gm. of refined whole yellow marrow. The same

9 Piersol, G. M., and Steinfield, E. Granulopenia (Granulocytopenia), with Special Reference to Classification and Benign Types, *Arch. Int. Med.* **49**: 578 (April) 1932.

10 Dennis, E. W. Experimental Granulopenia Due to Bacterial Toxins Elaborated in Vivo, *J. Exper. Med.* **57**: 993 (June) 1933.

11 Flipse, M. J. Personal communication to the authors.

person showed an increase from a normal total leukocyte count, of 7,000, to 21,000 (86 per cent polymorphonuclears) within twenty-four hours after taking a teaspoonful of the concentrate

CLINICAL OBSERVATIONS

The effect of our preparation on patients with granulocytopenia is illustrated in the following briefs of cases in which it was tested. These summaries and the data on the blood counts were taken from the records of the respective hospitals or attending physicians and are presented in chronological order. The diagnoses given are those of the attending physicians. Four of the patients (cases 1 to 4) were treated with material prepared in this laboratory, subsequent patients received a concentrate prepared by essentially the same method in the pharmaceutical department of Armour & Co.

CASE 1—Mrs. H. V. (a patient of Dr. E. M. Poser, Columbus, Wis.) was first seen on March 10, 1934. She complained of pain in the cervical, dorsal, lumbar and sacro-iliac regions, with accompanying difficulty in walking. Physical examination revealed no abnormality except pain and lessened mobility of the spine and in the sacro-iliac region.

The patient was given liver extract with iron orally until her return on March 14. A blood count at that time showed hemoglobin, 80 per cent, red blood cells, 4,800,000, and leukocytes, 2,600, with 27 per cent granulocytes. Treatment with yellow bone marrow concentrate was begun immediately—20 drops was given three times the first day, 10 drops, three times the second day, and 5 drops, three times a day, thereafter. The next count (March 23) showed hemoglobin, 80 per cent, red blood cells, 5,000,000, and leukocytes, 5,400, with 35 per cent granulocytes. The succeeding count, details of which are not available, was within the normal range. Clinical improvement followed immediately the restoration of a normal blood picture, and the patient was relieved of the arthritic condition. She remained in good health until her death from pneumonia two years later.

The diagnosis was chronic arthritis with leukopenia.

CASE 2—Miss E. D. (a patient of Dr. M. Simkin) was an office worker aged 34. She noticed pain and numbness about the gums and tongue on April 28, 1934. On the two following days the pain increased, the temperature rose to 101 F and was accompanied with malaise, nausea and vomiting and she was obliged to leave her work. When seen by her physician on May 1 she complained of severe pain in the mouth, general malaise and aching, lack of appetite and restlessness.

She had anemia in about 1922 and in 1930 and an infection of the upper respiratory tract, accompanied with loss of weight, an afternoon rise of temperature, diminished breathing and dulness over the bases of both lungs, with subcrepitant rales. Neither examination of sputum nor roentgenograms definitely established a diagnosis of tuberculosis. Four months' rest resulted in complete recovery and a gain in weight. The tonsils were removed in 1931. Two years later, purpuric spots and ecchymoses developed. A blood count showed hemoglobin, 70 per cent, erythrocytes, 4,000,000, leukocytes, 9,000, and platelets, 100,000. The symptoms abated with liver therapy, but she continued to have

occasional purpuric spots. In June 1933 she had abdominal pain, with albuminuria, but recovered after a week's rest in bed. Her symptoms had been present for three days and were increasing in severity. She had not taken aminopyrine.

Physical examination revealed no abnormality except swollen and spongy gums and bleeding ulcerations under the upper incisors and over the lingual aspect of the left molars. The temperature was 101.5 F and the pulse rate 100.

Local treatment was instituted. She felt somewhat better the following day but was weak and languid. The temperature was 100.5 F, and a blood count showed 4,000 leukocytes, which was thought to be a low count, but not alarming. The ulceration under the upper incisors had disappeared. The next day (May 3) the pain in the ulceration about the upper molars on the left side was so severe as to require morphine. The ulcer had enlarged and deepened and was covered with a white membrane.

The blood count on the morning of May 4 showed hemoglobin, 70 per cent, erythrocytes, 4,230,000, and leukocytes, 2,900, with 60 per cent lymphocytes and 38 per cent neutrophils. She was hospitalized and given liver extract and pentnucleotide parenterally. Ten cubic centimeters of pentnucleotide caused a severe reaction, and it was necessary to give subsequent injections in divided doses. Three cubic centimeters of liver extract was given parenterally every second day and 16 to 20 cc of pentnucleotide every day.

The patient's condition changed little during the two following days, the leukocyte count reached its lowest level on May 6 (1,500, with 36 per cent neutrophils). There was little change on the seventh day, blisters appeared on the lips on the eighth day and broke the following day, leaving painful indurated ulcers at their sites. Treatment with extralim was thereupon started, 4 capsules being given three times a day. The patient felt definitely better on May 12, although the ulcers had not changed in appearance. The blood count had improved, showing 3,400 leukocytes, with 63 per cent neutrophils. The temperature still ranged from 99 to 100 F. There was slow clinical improvement during the following days. On May 16 there were 5,700 leukocytes, with 76 per cent neutrophils. The use of liver extract was discontinued.

On May 20, with the leukocytes numbering 6,500, the ulcers in the mouth and on the lips showed definite evidence of healing. The patient strenuously objected to the injections of pentnucleotide, and the dose was reduced to 12 cc on May 21 and to 8 cc on May 22, when the leukocyte count was 4,150, with 84 per cent neutrophils. The ulcers were then almost completely healed. Treatment with pentnucleotide and extralim was discontinued on May 23.

The leukocyte count had fallen to 4,250 on May 24, and although the patient felt well and had no fever, the blood picture was not considered satisfactory. Two 0.5 Gm enteric-coated capsules¹² of the nonsaponifiable residue of yellow bone marrow were given and the dose was repeated the following day. On May 26 as the leukocyte count remained at 4,250, she was given yellow bone marrow concentrate (in oil), 105 drops per day. She was discharged from the hospital the following day, the count showing 4,500 leukocytes. On May 28 (forty-eight hours after the start of treatment with yellow bone marrow concentrate in oil) the leukocyte count was 7,500. The dose was reduced to 75 drops for one day and was then gradually reduced to 40 drops by June 23.

In order to test the potency of the concentrate, the medication was stopped from June 29 to July 5. The leukocyte counts were: June 29, 6,000, July 2, 5,800,

12 It was later learned that the capsules were too heavily coated and would not open in the gastro-intestinal tract.

and July 5, 4,000 Treatment with the concentrate (60 drops) was immediately resumed, and the next count (July 9) showed 7,500 leukocytes The yellow bone marrow concentrate was gradually withdrawn, and the blood count remained within normal limits

In March 1937 the patient had a recurrence but was seen before the sublingual ulcer had extended far With the use of yellow bone marrow concentrate the leukocyte count rose from 3,500 to 7,500 in less than seventy-two hours, and the angina was controlled

The diagnosis was recurrent agranulocytic angina (table 1 and chart 1)

CASE 3—Mrs L C, aged 56, a patient in the University of Chicago Clinics, entered the hospital on July 3, 1934, with pain in the lower part of the back and sciatica She had mastectomy for carcinoma of the left breast three years previously She returned in May 1934, with a local recurrence, she was given local roentgen therapy and was discharged on June 6 The blood count on May 15 showed hemoglobin, 80 per cent, erythrocytes, 5,200,000, and leukocytes, 7,400 The present symptom dated from about that time

Physical examination on July 3 revealed nothing significant except four or five small metastases in the operative scar on the left side of the chest The blood count showed hemoglobin, 75 per cent, erythrocytes, 4,370,000, and leukocytes, 4,050

From July 3 to 9 a total of 2,150 roentgens was given over the left side of the chest and the lumbosacral region, codeine, phenobarbital and aminopyrine (the average dose of the last was about 0.7 Gm per day) were given for sedation On July 9 the blood count showed 3,100 leukocytes, roentgen treatment was suspended Sedatives were given as before On July 13 the leukocyte count was 2,600, with 74 per cent polymorphonuclears The leukocyte count fell to 1,900 on July 15

Treatment with 1,250 roentgens was given between July 17 and 20 On July 21 the leukocyte count was 900, and on July 22, 850 She was given a transfusion of 500 cc of citrated blood Irradiation and treatment with aminopyrine were discontinued, and on July 23 treatment was started with yellow bone marrow concentrate, 35 drops three times a day The blood count on that day showed erythrocytes, 4,440,000, and leukocytes, 950, with 44 per cent polymorphonuclears, 2 per cent eosinophils, 9 per cent basophils, 35 per cent lymphocytes and 10 per cent monocytes

The total leukocyte count rose to 1,800 on July 26 and to 1,700 on July 27, with little change in the differential picture except a rise in the monocyte count to 20 per cent on July 26 On July 28 there was a sharp rise in the granulocyte count to 57 per cent of 1,900, the patient felt better The increase continued—July 30, 3,900 leukocytes, with 65 per cent neutrophils, July 31, 4,000 leukocytes with 71 per cent neutrophils, August 1, 3,600 leukocytes, with 77 per cent neutrophils She was discharged on August 2 for care at home The subsequent course is not known, except that she died some time later

The diagnosis was leukopenia associated with carcinomatosis (table 2 and chart 2)

CASE 4—Miss D S, an x-ray technician aged 24, was admitted to St Luke's Hospital on Oct 23, 1934 She complained of sore throat of twenty-four hours' duration and of increasing severity, malaise and chills She had had the disease of childhood with more than usual severity, repeated attacks of tonsillitis and dysmenorrhea for a long time She occasionally took aminopyrine for the latter but was uncertain as to the amount She had recently taken time off from her

TABLE 1—*E D, Patient of Dr M Simkin*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Mono- cytes, %	Eosino- phils, %	Baso- phils, %	Segmented Neutrophils, %
5/ 2/34			4,000					
5/ 4/34		4.23	2,900	60		1	1	38
5/ 5/34		4.57	1,950	64		1	1	33
5/ 6/34	a m		1,500	52			2	36
	p m		2,650	54	2	2		44
5/ 7/34			3,900	55	9	2	1	33
5/ 8/34			2,200	52				48
5/ 9/34			2,500	49		3	1	47
5/10/34		4.02	2,450	59		4		37
5/11/34			2,300	55				44
5/12/34			3,400	37				63
5/13/34			3,850	22		4		74
5/14/34			4,500	25				75
5/15/34			5,050	23		1		76
5/16/34			5,700	23		1		76
5/17/34			6,850	33				67
5/18/34			6,350	21				79
5/19/34		3.91	3,950	29				71
5/20/34			6,500					
5/21/34		4.42	4,100	17	2			81
5/22/34			4,150	16				84
5/23/34			5,450	27	1		1	71
5/24/34			4,250	27		3		69
5/25/34			4,200	33			1	61
5/26/34		4.27	4,250	30			1	71
5/27/34			1,500	24			2	74
5/28/34			7,500					
5/31/34			6,000	26	1		1	72
6/ 2/34			6,200					
6/ 3/34			6,100					
6/ 4/34			5,800					
6/ 7/34			6,300	28				72
6/ 9/34			6,500					
6/11/34			6,000					
6/21/34			6,100					
6/23/34			5,900					
6/26/34			5,600					
6/29/34			6,000	26				74
7/ 2/34			5,800					
7/ 3/34			4,000					
7/ 9/34			7,500					
7/12/34			6,500					
7/20/34			5,900	30				70

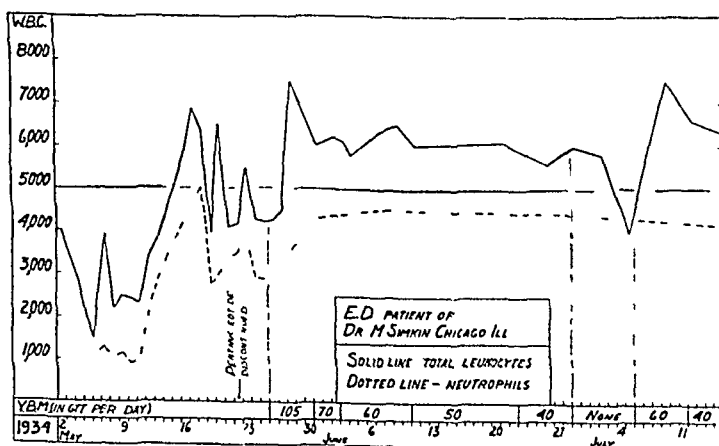
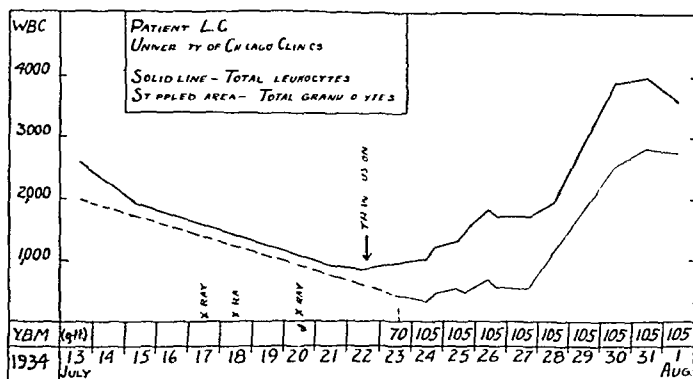


TABLE 2—*L C, Patient in University of Chicago Clinics*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils, %		Myelocytes
								Segmented	Metamyelocytes	
1/13/31		5.50	8,800							
5/15/34		5.20	7,400							
7/ 3/34		4.37	4,050							
7/ 9/34			3,100							
7/12/34		5.89	2,500							
7/13/34		4.40	2,600	17	5	3	1	74		
7/15/34			1,900							
7/21/34		3.90	900							
7/22/34		5.10	850							
7/23/34		4.44	950	35	10	2	9	44		
7/24/34	a m		1,000	52	11	2	3	22		
	p m		1,200	40	15	4	3	38		
7/25/34	a m		1,300	40	14	2	3	38	3	
	p m		1,500	45	16	2	4	30	2	1
7/26/34	a m		1,800	38	20	3	1	38		
	p m		1,700	46	14	5	2	33		
7/27/34	a m		1,700	45	13	3	2	37		
	p m		1,700	46	12	3	1	38		
7/28/34			1,900	27	12	2	2	57		
7/30/34			3,900	25	8	2		65		
7/31/34			4,000	20	6	2	1	71		
8/ 1/34		4.60	3,600	17	3	3		77		



work because of a "run-down and nervous" condition. The basal metabolic rate about a week before her present disturbance was -17 , since then she had been taking thyroid.

Physical examination revealed no abnormality except injection of the pharynx, cervical adenopathy and swelling of the right tonsillar area, suggestive of an abscess behind it. The temperature was 103.6°F . A blood count showed hemoglobin, 64 per cent, erythrocytes, 3,460,000, and leukocytes, 1,000, with 1 per cent neutrophils.

A transfusion was given, and treatment with liver extract and pentnucleotide was begun. She grew steadily worse, on the evening of October 25 the temperature reached 105.6°F (rectal). The white cell count on October 25 was 1,450 in the morning and 650 in the afternoon. After a transfusion (10 p m) there were 1,820 leukocytes. Yellow bone marrow concentrate was given, 5 cc for the initial dose at 11 p m, followed by 1.5 cc every four hours. The use of pentnucleotide and liver was discontinued. On the following day her condition was essentially unchanged, she was irrational at times. There was definite clinical improvement on October 27, with the temperature 102.4 to 104.4°F , and the throat somewhat

less painful. The next day showed continued clinical improvement, the temperature approaching normal and the leukocyte count being approximately doubled (3,800). The count rose rapidly—6,400 on the morning of October 29, 7,200 in the afternoon, 9,850 (54 per cent neutrophils) on the morning of October 30 and 11,250 in the afternoon. A small ulcerated area developed near the right tonsil, and later a small ulcer appeared under the tongue. Pus was draining from around the upper pole of the right tonsil. The throat remained painful until November 6, when a localized abscess on the right side of the neck was opened and drained. The white cell count was about 15,000.

After drainage of the abscess the patient improved rapidly. Treatment with yellow bone marrow concentrate, the dose having been reduced to 0.5 cc every four hours, was discontinued on November 9 (the eighteenth day). By November 13 the mouth and throat looked normal, and the neck was healed. The white cell count varied between 9,000 and 15,000, with about 45 per cent neutrophils (mostly polymorphonuclears), until her discharge on November 16. The final diagnosis was agranulocytosis (table 3 and chart 3).

CASE 5—A single woman (a patient of Dr. E. M. Birchwood), an office worker aged 38, came to the office on May 14, 1935, with a complaint of fatigue, sleeplessness and poor appetite. She was unable to do the work she had previously been doing. She had been worrying over illness and death in her family. There was nothing significant in her past history, her general health had been good except for headaches since an infection of the upper respiratory tract in January 1935. There appears no statement in regard to the use of aminopyrine.

Physical examination revealed only a mildly inflamed mouth and pharynx and a coated tongue. The laboratory findings were normal except that the blood count showed hemoglobin, 80 per cent, erythrocytes, 4,140,000 and leukocytes, 2,800, with 62 per cent polymorphonuclears.

She was asked to return in a week, to allow for completion of laboratory tests. On May 21 the white cell count was unchanged—2,900, with 68 per cent polymorphonuclears. Treatment with yellow bone marrow concentrate was started, 1 cc three times a day, and she was told to rest in bed. When seen one week later she said she felt much better and was out of bed. The leukocyte count was 3,600, with 67 per cent polymorphonuclears. The dose of yellow bone marrow concentrate was increased to 5 cc three times a day for one day and then was 5 cc daily.

When seen on June 4 the patient said she felt well but was somewhat weak. A blood count revealed 7,225 leukocytes, with 72 per cent polymorphonuclears. She returned to work, on June 11 the blood showed 7,600 leukocytes and a normal differential picture. When seen again on June 18 she felt well. As the white cell count was normal (8,200), the use of yellow bone marrow concentrate was discontinued. The further progress was uneventful, the count remained normal.

The diagnosis was chronic leukopenia (table 4 and chart 4).

CASE 6—Mrs. H. F., a housewife aged 31 (a patient of Dr. D. E. Markson), was admitted to the Norwegian-American Hospital on June 14, 1935, with complaints of malaise, fever and sore throat. She had been well until the past month. About May 15 she had a tonsillectomy. On May 22 an abscessed upper molar was extracted. About June 1 she had sore gums, a temperature of 101 to 103 F, headache and malaise. She was given four injections of neoarsphenamine, but the lesions were not improved by this or by mouth washes. Several pieces of tissue were removed from the floor of the mouth a few days before she entered the hospital. No statement appears regarding the use of aminopyrine.

TABLE 3—D S, Patient of Dr N C Gilbert, St Luke's Hospital

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Neutrophils, %			Myelocytes, %	Promyelocytes, %
						Segmented	Band form	Metamyelocytes		
10/23/36	a m	3 46	1,000	99 0		1 0				
	p m		1,350							
10/24/36		3 52	1,050	99 0	1 0					
10/25/36	a m	4 04	1,450	96 0	2 0	2 0				
	p m		650							
	p m		1,820							
10/26/36	a m	3 50	900	94 0	4 0	2 0				
	p m		800							
			1,850							
10/27/36		3 68	2,000	86 0	7 0	4 0	3 0			
			1,100							
10/28/36		4 11	3,800							
10/29/36	a m	3 75	6,400	36 0	6 5	24 0	28 0	5 5		
	p m		7,200							
10/30/36	a m	3 92	9,850	43 0	3 0	37 5	14 0	2 5		
	p m		11,250							
10/31/36	a m	3 89	9,000	31 0	3 0	32 5	19 5	8 5	1	4 5
	p m		7,350							
11/ 1/36		4 00	8,750	36 5	2 5	28 5	22 0	8 0	2	0 5
11/ 2/36	a m		9,150							
	p m		12,550	45 0	4 0	32 0	12 0	4 0	3	
11/ 3/36	a m	3 92	10,650	41 0	3 0	35 0	18 0	1 0	2	
	p m		11,300							
		4 02	12,300	40 0	1 0	52 0	6 0	1 0		
11/ 5/36	a m	4 11	17,450	31 0	2 5	57 5	8 0	1 0		
	p m		18,100							
11/ 6/36	a m	4 20	14,550	28 5	2 0	66 0	3 5			
	p m		15,500							
11/ 7/36	a m	4 08	12,450	36 0	0 5	62 0	1 5			
	p m		13,400							
11/ 8/36		4 08	11,350	57 0	2 0	39 5	1 5			
11/ 9/36	a m	4 07	9,850	51 5	1 5	47 0				
	p m		9,050							
11/10/36	a m	4 00	10,050	55 0	4 0	39 0	1 5	1 5		
11/12/36	p m		10,250							
	a m	4 12	9,400	50 0	4 0	42 5	3 5			
	p m		11,300							
11/13/36	a m	4 09	12,500	55 5	2 5	41 0	2 0			
	p m		13,250							
11/14/36	a m	4 11	14,450	47 0	6 0	47 0				
	p m		12,300							
11/15/36	a m	4 21	10,700	51 5	2 5	45 5	1 5			
	p m		10,600							
11/16/36	a m	4 26	13,250	55 0	2 0	43 0				
	p m		11,200							

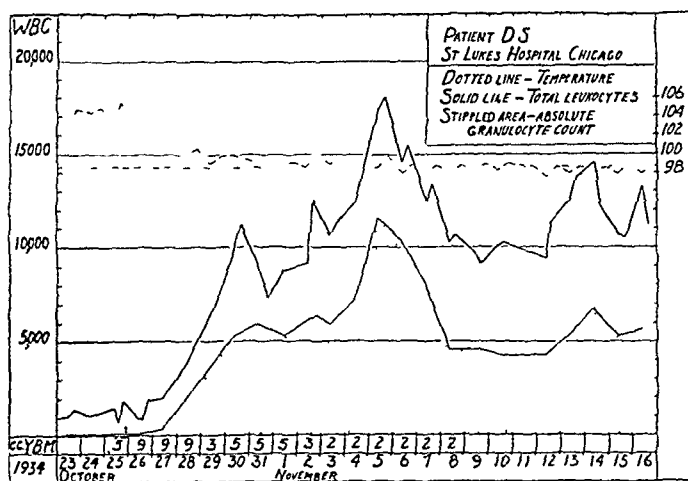
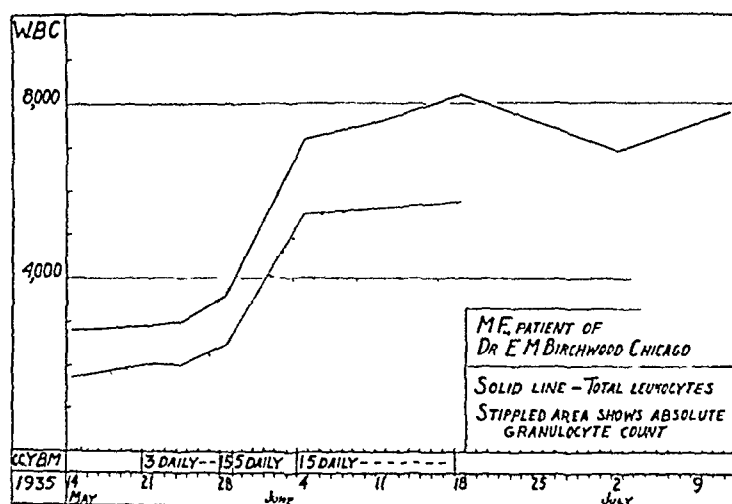


TABLE 4—*M F, Patient of Dr E M Birchwood*

Date	Erythrocytes, Million	Leuko cytes	Lympho cytes, %	Mono cytes, %	Eosino phils, %	Neutrophils, %	
						Baso phils	Seg mented
5/14/36	4 14	2,800	35	3			62
5/21/36		2,900	30		1	1	68
5/24/36	4 30	3,000	30	3	1	2	64
5/28/36		3,600	32		1		67
6/ 4/36		7,225	24		4		72
6/11/36	4 24	7,600	22	4	2	2	70
6/18/36		8,200	30		1	1	68
7/ 2/36		6,900					
7/12/36		7,800					
7/23(?)	4 24	6,425	28		1	1	70



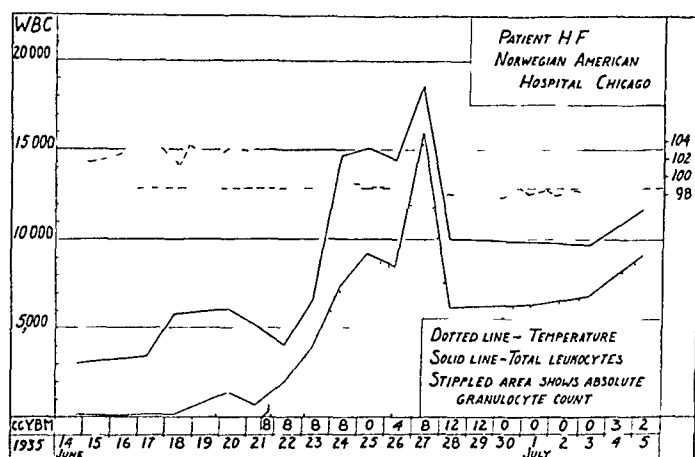
Physical examination revealed an ulcerated area on the left side of the mouth and under the tongue covered with necrotic tissue. The gingival margins were red, the throat was slightly reddened and the temperature was 101.8 F. Other physical findings were normal. The blood count showed hemoglobin, 85 per cent, erythrocytes, 3,860,000, and leukocytes, 2,850 and 3,250, respectively, on two occasions, with over 90 per cent lymphocytes.

The patient was given pentnucleotide, 10 cc twice a day, beginning on June 15, but had moderate to severe reactions to the injections, and she protested at the treatment. The leukocyte count rose on June 18 to 20 to about 6,000, with 23 per cent granulocytes, but fell again on the two following days. The oral lesions were extending, and the clinical picture was essentially unchanged. On June 21 the white cell count was 5,100, with 15 per cent polymorphonuclears. Treatment with pentnucleotide was discontinued, and yellow bone marrow concentrate was given, beginning with 5 cc at 6 p. m. On the following day the temperature fell below 100 F for the first time, and the granulocyte count rose to 50 per cent.

On June 23 (forty hours after treatment with yellow bone marrow concentrate was begun) the leukocyte count was 6,600, with 59 per cent neutrophils. The general condition was improved. Twenty-four hours later there were 14,650 leukocytes, with 50 per cent polymorphonuclears, and the temperature was normal. The ulcer in the floor of the mouth, which had extended to the gum between the lower incisors on the left, began to show resolution. A slough was forming on the left side of the upper gingival margin where the tooth was extracted. The

TABLE 5—*H F, Patient of Dr D E Markson, Norwegian-American Hospital*

Date	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Polymorphs, %	Segmented Neutrophils, %	Unclassified
6/14/35	3.86	3,250	90		1	9
		2,850	94		2	4
6/16/35		3,350	96		0	4
6/17/35		3,400	70		1	29
6/18/35		7,300	50		1	49
		4,250	53		0	47
6/20/35	3.84	6,060	76	1	12	11
6/21/35		5,100	48		14	38
6/22/35		4,050	50	9	39	2
6/23/35		6,600	32		53	15
6/24/35		14,650	30		50	20
6/25/35		15,050	36		56	8
6/26/35		14,350	36		59	5
6/27/35	4%	18,650	11		80	9
6/28/35		10,050	35		61	4
7/1/35		9,800	32		64	4
7/3/35		9,650	30		69	1
7/5/35		11,700	23		77	



dose of yellow bone marrow concentrate was changed to 4 cc three times a day. The leukocyte count continued at a high level (14,000 to 18,000) until June 28, when it was 10,050, with 61 per cent polymorphonuclears. The temperature was normal, the clinical condition was good and the infection in the mouth was definitely arrested. The gums were pink.

On July 2 necrotic tissue had come away, revealing the great depth of the ulcer, the posterior aspects of the roots of the incisors were visible almost to their tips. The patient's condition was steadily improving. The dose of yellow bone marrow concentrate was reduced to 1 cc twice a day for two days and was then discontinued. The patient returned to her home on July 5. The blood picture since then has been normal, and the oral lesions are entirely healed.

The diagnosis was agranulocytosis (table 5 and chart 5).

CASE 7—Mrs. E. S., a housewife aged 32 (a patient of Dr. T. E. Walsh), was admitted to the Billings Hospital, University of Chicago Clinics, on April 3, 1936, complaining of sore throat, fever, bleeding from the mouth, deafness and diarrhea. She had had the sore throat for two weeks and had been given aminopyrine and allonal (allylisopropylbarbituric acid with aminopyrine) by another physician. The deafness, bleeding and diarrhea were of a few days' duration. She had had no other illness.

Physical examination revealed ulceration and bleeding in the gingivolabial fold on both sides of the upper jaw. The tonsils were swollen and ulcerated and the left one was bleeding; the odor was foul. The posterior wall of the pharynx was covered with a blood clot. The patient could not hear the spoken voice. The temperature was 105 F. A blood count showed erythrocytes, 3,200,000, and leukocytes, 800 to 1,000, no granulocytes were seen.

The patient was given a transfusion of 550 cc of citrated blood, and treatment with yellow bone marrow concentrate was begun, with 5 cc every four hours for twenty-four hours then 5 cc four times a day. Pentnucleotide also was given 20 cc twice a day. There was little change on the following day, but on April 5 the leukocyte count rose from 1,600 at 10 a. m. to 4,800 at 10 p. m., with many immature granulocytes. A transfusion of 550 cc of citrated blood at 8 p. m. may have contributed slightly to this rise. The patient seemed somewhat better clinically. On April 6 the blood picture was much improved: 9,700 leukocytes at 10:30 a. m., with 85 per cent neutrophils, mostly immature, 11,400 at 5 p. m., with 79 per cent neutrophils, of which 58 per cent were polymorphonuclears. The dose of yellow bone marrow was reduced to 2 cc four times a day, and the dose of pentnucleotide was reduced to 10 cc twice a day (omitted on April 8).

By April 7 the count had risen to 19,400, with 79 per cent neutrophils. Bleeding had stopped, even on removal of necrotic sloughs. The left side of the superior maxilla was denuded and showed some necrosis. The general condition was definitely better, the temperature approaching normal. Treatment with pentnucleotide was discontinued on April 11. By April 12 the leukocyte count was 30,000, with 88 per cent neutrophils, and the temperature was normal. The patient felt much better and could hear the spoken voice. The use of yellow bone marrow concentrate was discontinued on April 14. The leukocyte count fell to 18,100 on April 15.

The general condition improved steadily, and the patient was discharged on April 25. On May 28, when two molars and a sequestrum were removed from the left side of the upper jaw, the leukocyte count was 9,000, with 57 per cent polymorphonuclears.

The diagnosis was agranulocytic angina (table 6 and chart 6).

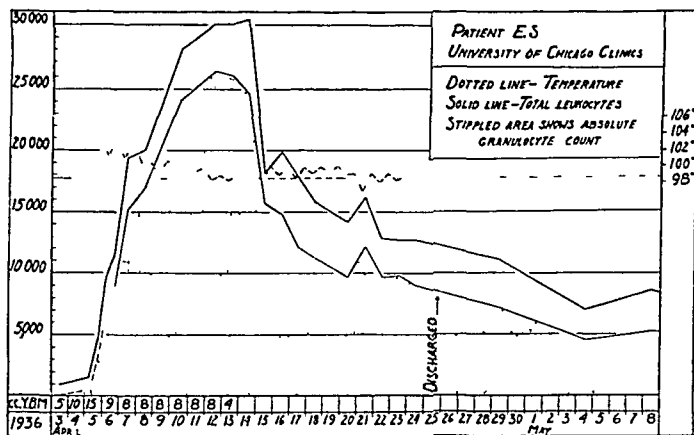
CASE 8—A woman office worker aged 29 (a patient of Dr. E. R. Stoch) complained on April 20, 1936, of weakness, susceptibility to fatigue, a noticeable lack of vigor and also a severe local and systemic reaction to smallpox vaccination (given April 10). She had been ill for six months with a condition characterized by deficiency of the leukocytes six years previously. This was said to follow obstinate ulcerations resulting from superficial injuries. The patient had periods of extreme nervous irritability, periodic migraine and occasional insomnia. No statement appears regarding the use of aminopyrine.

Physical examination showed that the tonsils were red and partly covered with a gray deposit. There was slight cervical adenopathy, and the splenic area was slightly tender. The blood count showed erythrocytes, 4,750,000, and leukocytes, 3,650, with 10 per cent lymphocytes, 9 per cent monocytes, 4 per cent band cells and 77 per cent mature neutrophils.

The patient returned the following day (April 21), and the leukocyte count was 3,300, with 63 per cent neutrophils. Yellow bone marrow concentrate was given in 2.5 cc doses at four hour intervals for four doses. The leukocyte count on the morning of April 22 was 4,800, with 67 per cent neutrophils and 20 per cent monocytes. Three 2.5 cc doses of yellow bone marrow concentrate were given. At 6:30 p. m. she had an attack of cyanosis, which was relieved by dextrose and insulin. At 11 p. m. there were 7,300 leukocytes.

TABLE 6—*E S*, Patient of Dr. T E Walsh, University of Chicago Clinics

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils, %			Myelocytes, %	Promyelocytes, %	Myeloblasts, %	Plasma Cells, %
								Segmented	Band Form	Metamyelocytes				
4/ 3/36	p m	3 20	1,000	100 0										
4/ 4/36	a m		1,300											
	p m		1,400											
4/ 5/36	a m		1,600											
	p m		4,800											
4/ 6/36	a m		9,700	12 0	3 0			22 0	14 00	21 00	2 0	23 0	3	
	p m		11,400	20 0	1 0			58 0		4 00	15 0			2
4/ 7/36		3 25	19,400	9 0	12 0			53 0	8 00	7 00		3 0	1	
4/ 8/36			20,000	8 0	7 0			44 0	15 00	8 00	17 0		1	
4/10/36			28,000	7 0	6 0			30 0	26 00	20 00	10 0		1	
4/12/36			30,000	12 0				27 0	17 00	34 00	10 0		1	
4/13/36			30,000	13 0				49 0	2 00	36 00				
4/14/36			30,400	16 0	2 0			58 0	5 00	18 00				
4/15/36		3 30	18,100	13 0				60 0	4 00	16 00	1 0			
4/16/36			19,900	21 0	4 0			54 0	5 00	14 00	2 0			
4/17/36			17,800	21 0	11 0	1 0		58 0		9 00				
4/18/36			15,800	21 0	7 5	0 5		64 5		6 00	0 5			
4/20/36			14,100	24 5	7 0	1 0		65 5		2 00				
4/21/36			16 200	17 0	8 0	1 0		73 2	0 80					
4/22/36		3 53	12,900	18 5	6 5	2 5		70 5	0 25	1 75				
4/23/36			12,700	17 0	6 0	2 5		74 5						
4/24/36			12,700	23 5	6 0	2 0		68 5						
4/29/36			11,000	27 0	7 0	0 5	2	63 0				0 5		
5/ 4/36			7,000	35 0	10 0			55 0						
5/ 8/36			8 500	32 0	4 0			62 0						
5/14/36			7,400	27 0	10 0	1 0	1	60 0						



On April 23 the leukocyte count reached its maximum, 11,400, with 76 per cent segmented neutrophils. This was an increase of over 200 per cent in the forty-four hours since the administration of the initial dose of yellow bone marrow concentrate. The subsequent course was uneventful. Yellow bone marrow concentrate was given in doses up to 24 drops daily and finally was discontinued.

The diagnosis was leukopenia (table 7 and chart 7).

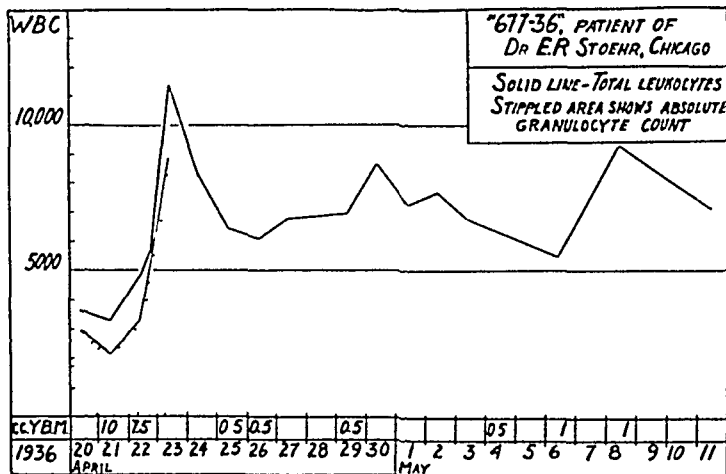
CASE 9—Miss P. M., aged 37 (a patient of Drs. P. E. Hopkins and W. W. Sittler), was admitted to the Evangelical Hospital on June 26, 1936, because of sore throat, malaise and fever. She had been in good health until May 1, when

sore throat and mild fever developed. This condition persisted for about three weeks. On June 22 she again had a sore throat, with a chill and general aching. By June 25 both tonsils were red, with necrotic spots, there were necrotic spots on the gums also.

Physical examination revealed nothing abnormal outside the mouth and throat. "Necrotic areas were noted in the crypts of both tonsils, and a white thin mem-

TABLE 7—Patient of Dr. E. R. Stoeck

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils %	
								Segmented	Band Form
4/20/36		4.75	3,650	10	9			77	4
4/21/36			3,300	6	14		2	57	6
4/22/36	10 a m		4,800	12	20		1	62	5
	8 p m		5,770						
	11 p m		7,200						
4/23/36	8 a m		11,400	15	6	2		76	

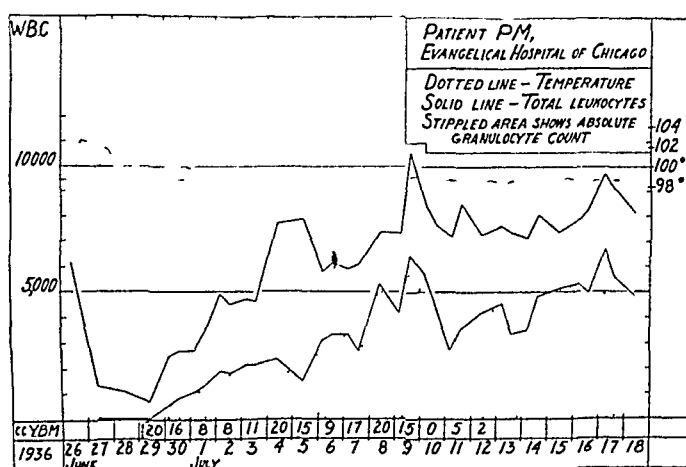


brane was noted over the anterior right pillar and on the left posterior pharyngeal wall. There was an inflammatory area about the membrane extending over the anterior pillars and the uvula. Small necrotic areas also appeared in the gingival margins of several teeth. The submaxillary lymph nodes were moderately enlarged. The blood count at the time of entry was not significant—erythrocytes, 3,760,000, hemoglobin, 75 per cent, and leukocytes, 6,150. No differential count was made.

Treatment was largely palliative for the first two days, 60 cc of nonspecific human serum, 10 grains (0.65 Gm) of aminopyrine and 2 cc of liver extract parenterally were given in addition. The lesions were somewhat improved on the second day, but the leukocyte count had fallen to 1,300, with 98 per cent lymphocytes. On June 28 the leukocyte count was 1,100, the patient was weak and the lesions had spread to the uvula. Pentnucleotide was given, 10 cc twice a day. On the fourth day (June 29) the leukocyte count had dropped to 650, with 1 per cent band cells and 99 per cent lymphocytes. The uvula was swollen to twice its normal size and was covered with membrane, the tonsils were very red and partly covered with membrane. The temperature was 101.8 F. Yellow bone marrow concentrate was ordered, 5 cc every four hours for twenty-four hours and then 2 cc four times a day.

TABLE 8—*P M, Patient of Dis P E Hopkins and W W Sittler, Evangelical Hospital of Chicago*

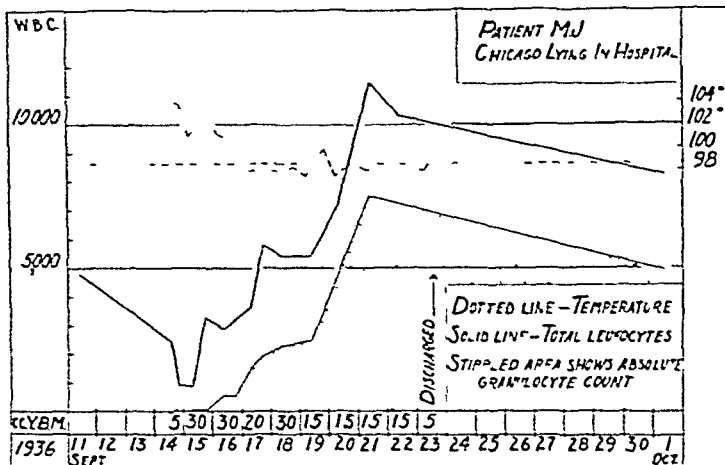
Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Basophils, %	Neutrophils, %			Mycetocytes, %	Plasma Cells, %
							Segmented	Band form	Metamyelocytes		
6/26/36		3.76	6,150								
6/27/36		3.61	1,300	98				1	1		
6/28/36		4.05	1,100								
6/29/36			650	99				1			
6/30/36	a m		2,450	74			2	12	8	2	2
	p m	3.71	2,650	79	8		21		6		
7/ 1/36	a m	3.82	2,650	60			27	7	3		
	p m	3.96	3,400	58	3		19	16	4		
7/ 2/36	a m	3.08	1,900	60	1		13	21	3	1	1
	p m	3.71	4,500	60			15	11	10	4	
7/ 3/36	a m	4.00	4,700	64			12	16	5	1	1
	p m	4.07	4,650	64			16	12	6	2	
7/ 4/36		4.10	7,700	69			20	6	4	1	
7/ 5/36		4.12	7,850	81				3			
7/ 6/36	a m	4.12	5,800	48			47	5			
	p m	4.075	6,100	46	3		48	3			
7/ 7/36	a m	4.15	5,900	39	1		54	3			
	p m	4.99	6,050	49	7		40	4			
		4.20	7,350	28	4		64	1			
7/ 9/36	a m	4.23	7,300	38	3		54	3	1		2
	p m	4.13	10,600	38	1		31	29			
7/10/36	a m	4.25	8,400	31			17	16	3		1
	p m	4.25	7,650	10			35	20	1	2	1
7/11/36	a m	4.21	7,200	60	2		30	8			
	p m	4.45	8,500	58			21	16	2		
7/12/36	a m	4.26	7,200	12			28	20	6	4	
7/13/36	a m	4.15	7,600	40			28	28	4		
	p m	4.45	7,350	52	2		21	18	2	2	
7/14/36	a m	4.30	7,150	50			42	6	1		
	p m	4.22	8,050	40		1	27	14	10	8	
7/15/36		4.16	7,350	30		1	27	32	6	4	
7/16/36	a m	4.25	7,900	32			48	14	1	2	
	p m	4.10	8,350	40			42	8	4	6	
7/17/36	a m	4.40	9,700	20		1	51	18			
	p m	4.27	9,100	38			38	10	10	4	
7/18/36		4.35	8,100	40		2	12	10	4	2	



On June 30 the white cell count in the morning was 2,450, with 24 per cent neutrophils, and had risen by evening to 2,650, with 33 per cent neutrophils, mostly segmented. The condition of the throat was greatly improved, much of the membrane having disappeared. The temperature fell below 100 F, the general condition

TABLE 9—*M J, Patient in Chicago Lying-In Hospital*

Date	Time	Erythrocytes, Million	Leuko- cytes	Lympho- cytes, %	Mono- cytes, %	Baso- phils, %	Neutrophils, %			Myelo- cytes, %
							Seg- mented	Band Form	Meta- myelo- cytes	
9/11/36			4,800							
9/14/36	5 p m		2,400							
	10 p m		925							
9/15/36	a m	4.52	1,000	90.0	7.0		3.0			
	p m		3,500	83.0	12.0		2.0	2.0	1.0	
9/16/36	a m		2,900	70.0	11.0		6.0	10.0	2.0	1.0
	p m		3,200	76.0	7.0		5.0	9.0	4.0	1.0
9/17/36	a m		3,700	51.0	6.5		17.0	14.5	5.5	5.0
	p m		5,800	62.0	4.5		8.0	14.0	9.0	2.5
9/18/36			5,400	72.0	6.5		16.5	13.0	7.0	5.0
9/19/36			5,400	70.5	5.0	0.5	34.0	4.0	4.0	2.0
9/21/36			11,500	31.0	4.0		52.0	12.0	0.5	0.5
9/22/36			10,300	28.0	2.0		62.0	8.0		
10/1/36		4.12	8,200	35.0	5.0		60.0			
11/20/36		4.68	6,400	35.0	12.0		54.0			



was better. The clinical and hematologic pictures continued to improve. The dose of pentnucleotide was reduced to 10 cc daily on July 2. There was an abrupt increase in the absolute lymphocyte count on July 4, but this was followed shortly afterward by a corresponding rise in the granulocyte count.

On July 9 the leukocyte count reached 10,600, with 61 per cent neutrophils. Treatment with yellow bone marrow concentrate and pentnucleotide was discontinued. There was an abrupt fall in the total leukocyte and granulocyte counts—7,200 leukocytes, with 38 per cent neutrophils on July 11. Yellow bone marrow concentrate was given 5 cc daily on July 11 and 12. The neutrophil count rose immediately to 58 to 60 per cent. With the use of bone marrow concentrate again discontinued, the neutrophil count again fell below 50 per cent. The blood picture returned to normal shortly, and the patient was discharged in good condition on July 18. The subsequent course was uneventful.

The diagnosis was agranulocytic angina (table 8 and chart 8).

CASE 10—Mrs. M. J., aged 41, had attended the outpatient clinic of the Chicago Lying-In Hospital. She was admitted to the hospital on Sept. 14, 1936, with acute tonsillitis and pharyngitis and a temperature of 104°F.

In the past she had had an appendectomy, excision of the left ovary, gastric ulcer and gonorrhea. She had had dysmenorrhea, menorrhagia and probably chronic pelvic inflammation for a long time. She was seen in the outpatient

department on September 11 because of vaginal bleeding of ten days' duration. She had been taking a proprietary preparation containing aminopyrine for menstrual pain. The blood picture at that visit showed cell volume, 41 per cent, hemoglobin, 14.8 Gm, and leukocytes, 4,800.

Physical examination revealed pronounced dark redness of the lateral pharyngeal walls and tonsillar pillars, but no ulceration or membrane. When examined three days previously the throat had been normal. Other findings were normal except for the gynecologic conditions, which probably were not connected with the present illness.

On September 14, the day of entry, the leukocyte count was 2,400 at 5 p. m. and 925 at 10 p. m. Treatment with yellow bone marrow concentrate was started immediately, 5 cc every four hours. No other hematopoietic stimulant was given. The throat showed little change on the following day, there were small necrotic patches on each tonsil. In the morning the leukocyte count was 1,000, with 90 per cent lymphocytes, 7 per cent monocytes and 3 per cent polymorphonuclear neutrophils. By evening there were 3,300 leukocytes, with little change in the differential picture. On September 16 the patient was improved, the throat looked and felt better and the temperature was falling. The neutrophil count had increased to 19 per cent of 2,900 leukocytes.

There was marked improvement on September 17, in the morning the blood count showed 3,700 leukocytes, with 5 per cent myelocytes, 5.5 per cent metamyelocytes, 14.5 per cent band cells and 17 per cent segmented neutrophils. In the evening the leukocyte count was 5,800, with 33.5 per cent neutrophils. The temperature was normal. The clinical and blood pictures continued to improve. The dose of yellow bone marrow concentrate was reduced to 5 cc three times a day on September 19. On September 21 the leukocyte count reached its maximum—11,500, with 65 per cent neutrophils, of which 52 per cent were segmented, 12 per cent were band cells and 1 per cent were myelocytes and metamyelocytes.

The patient was discharged in good condition on September 23. Subsequent counts on October 1 and November 21 were within normal limits.

The diagnosis was agranulocytic angina (table 9 and chart 9).

COMMENT

Yellow bone marrow concentrate was used without success in seven cases of leukopenia, not true agranulocytosis. One patient, a woman aged 76 with diabetes of five years' standing, was treated at the University of Chicago Clinics for agranulocytosis (without angina) and abdominal pain. She was given yellow bone marrow concentrate and there was some evidence of myeloid activity after sixty hours but she died on the sixth day of hospitalization without significant improvement in the blood picture. At autopsy the appendix showed necrotic ulcers, with serofibrinous periappendicitis and mononuclear cell infiltrations without polymorphonuclear response.

In three of these cases the diagnosis was aplastic anemia. Death occurred in the case of a man aged 65 and that of a 5 year old girl, in her case the etiologic factor being obscure. In the third patient, a woman of 35, the condition developed after antisyphilitic treatment, but she ultimately recovered. In none of these three cases was there evidence of

hematopoiesis as a result of treatment with yellow bone marrow. In the other three cases, in which the tentative diagnosis was leukemia, there was no response to the administration of the concentrate.

In cases of acute agranulocytic angina (malignant neutropenia) the condition of the patient is often so critical that any or every hopeful therapy is started, e. g. blood transfusion and the use of sodium pentnucleotide, liver extract and normal or immune serums. Transfusion has been considered to be of transitory value, if any.¹² Jackson and Parker¹³ reported beneficial results after the parenteral administration of sodium pentnucleotide and observed that the response of the white blood cells follows four to six days after the beginning of treatment. Liver extract is frequently given, but aside from its bolstering effect on erythropoiesis it is of doubtful value.¹⁴ Consequently for our six patients with acute agranulocytosis, yellow bone marrow concentrate was used as the sole granulocytopoietic medication in one case and coincidentally with pentnucleotide in two cases. In three cases treatment with pentnucleotide was discontinued and yellow bone marrow concentrate was given after two to sixteen days.

Summary of the Data—Case 1. The leukocyte count more than doubled in nine days while the patient was given yellow bone marrow concentrate.

Case 2. This patient with acute agranulocytic angina did not show a definite increase in the total leukocyte and granular leukocyte counts until eight days after treatment with pentnucleotide was begun. After the initial rise the total white cell count was not maintained above 5,000. Clinical recovery was slow, about sixteen days elapsed before there was definite resolution of the ulcers, as compared with the rapid recovery in the cases in which yellow bone marrow concentrate was given. In this case the leukocyte count rose from 4,250 to 7,500 forty-eight hours after the use of yellow bone marrow concentrate was begun. The level was maintained at 6,000 for four weeks. Seven days after the concentrate was withdrawn the count had fallen to 4,000, but seventy-two hours after the readministration of yellow bone marrow concentrate it rose again to 7,500. These two responses to marrow therapy together with the patient's immediate recovery from an attack in 1937, point to active stimulation of the hematopoietic system by the unsaponifiable residue.

Case 3. This patient showed a fourfold increase in the leukocyte count during eight days of treatment with yellow bone marrow concentrate. The differential picture changed from 44 to 71 per cent neutro-

13 Jackson, H. and Parker, F. Agranulocytosis. Its Etiology and Treatment, New England J. Med. **212** 137 (Jan. 24) 1935.

14 Reich, C., and Reich, E. Further Studies in the Treatment of Agranulocytosis, J. Lab. & Clin. Med. **22** 503 (Feb.) 1937.

phils It would be difficult to interpret this as a response to the discontinuation of 1000 röntgen treatment, since in the eight day period from July 9 to 17 when 1000 röntgen therapy was not given there was no evidence of hematologic recovery

Case 4 Pentnucleotide and liver extract were used for two days without apparent benefit, forty-eight hours after their use was discontinued and bone marrow therapy was instituted there was an abrupt and sustained rise in the leukocyte count, followed by clinical recovery of the patient In this patient, as in the others with a febrile condition, the temperature approached normal as the leukocyte count rose to or above a normal level

Case 5 This patient with chronic leukopenia gave a definite response (100 per cent increase) when the dose of yellow bone marrow concentrate was increased from 1 cc three times a day to 5 cc three times a day and then was reduced to 5 cc daily Her condition after three weeks of treatment was improved to the point that the blood count was normal and she returned to work

Case 6 Seven days of treatment with pentnucleotide produced no clinical improvement, the rise in the leukocyte count on the fifth to seventh days was not sustained on the eighth and ninth Pentnucleotide therapy was discontinued and yellow bone marrow was given, forty hours later the leukocyte count was 6,600, with 53 per cent neutrophils The patient's reactions to the parenteral administration of pentnucleotide were so severe that she was at the point of refusing further injections The prolonged period of granulocytopenia (June 14 to 21) during treatment with pentnucleotide evidently permitted the extension of the ulcerated areas, which later became necrotic

Case 7 Both yellow bone marrow and pentnucleotide were given from the first day of hospitalization Here again the leukocyte response in forty-eight hours was marked and sustained, in contrast with the four to six day response to pentnucleotide when given alone

Case 8 In this case, as in case 5, the differential count was normal but there was an absolute depression of all leukocytic elements The white cell count rose from 3 300 to 11 400 in forty-four hours

Case 9 Twenty-four hours after the initial dose of yellow bone marrow concentrate the leukocyte count had risen from 650 to 2,650, as this was only forty-eight hours after the beginning of pentnucleotide treatment it seems permissible to ascribe the response to the yellow bone marrow therapy Of special interest is the decrease in the granulocyte count after the discontinuance of treatment with pentnucleotide and yellow bone marrow concentrate on July 9 with the increase in the granulocyte count when bone marrow concentrate was given again two days later (chart 8)

Case 10 This patient received yellow bone marrow concentrate only. The leukocyte response came twenty-four to thirty-six hours after the beginning of treatment, clinical improvement was evidenced by the following day, and the patient made an uneventful recovery.

SUMMARY AND CONCLUSIONS

Four patients with leukopenia and six with agranulocytic angina (malignant neutropenia),¹⁵ all women, were treated with yellow bone marrow concentrate per os, all recovered. Those with acute leukopenia showed clinical and hematologic improvement at the end of forty to forty-eight hours as a rule. The initial rise continued to the level which might be expected from the nature of the local lesions, and in no case was there a recurrence of the depression of the blood cells or clinical symptoms during the period of treatment. Although it was not always possible to use the yellow bone marrow concentrate alone, the evidence indicates that it has granulocytopoietic activity sufficient to bring about a normal blood picture when used in cases of agranulocytic angina and of some other leukopenias. Whether used alone or jointly with other medication it usually causes a response in forty to forty-eight hours, the interval when sodium pentnucleotide is used is stated to be four to six days. The case of agranulocytosis in which there was no response to therapy with yellow bone marrow was of such a nature (age and complications) as not to invalidate our other findings.

From these clinical tests it is concluded that the yellow bone marrow concentrate contains a substance or substances which act to stimulate the maturation or liberation of leukocytes of the granulocyte series. Clinical recovery in cases of leukopenia or agranulocytic angina coincides with or follows immediately after the restoration of a blood picture consistent with the severity of the local lesions. These results confirm the fundamental clinical observations of Dr. Watkins made on patients treated with whole yellow bone marrow. They establish the activity of a concentrate devoid of the bulky inert neutral fats which make whole bone marrow unpleasant for clinical use.

Armour & Co. gave the fellowship which made this work possible and supplied some of the materials used. A number of physicians cooperated by affording us the opportunity to make clinical tests.

15 Since this paper was written another patient with agranulocytic angina (following the use of aminopyrine), a man of 41, has been treated with yellow bone marrow concentrate and pentnucleotide, with hematologic recovery.

VARIATION IN CREATINE CONTENT OF HUMAN CARDIAC AND VOLUNTARY MUSCLE AT AUTOPSY

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The discovery of phosphocreatine and of the part played by this complex in muscular contraction has brought to light one of the major functions of creatine. It appears that the breakdown of phosphocreatine furnishes energy for the contraction,¹ that the amount of breakdown is concerned with the excitability of the muscle² and that this compound also acts as a buffer in the chemical reactions of the muscular processes³

Submitted for publication, July 29, 1937

Aided by a grant from the Josiah Macy Jr Foundation

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A report of this work was presented before the Cleveland Section of the Society for Experimental Biology and Medicine, March 8, 1935 (Linegar, C R, and Myers, V C. Further Studies on the Creatine Content of Heart Muscle, *Proc Soc Exper Biol & Med* **32** 1016, 1935)

1 (a) Rose, W C. The Metabolism of Creatine and Creatinine, in Luck, J M. *Annual Review of Biochemistry*, Stanford University, Calif, Stanford University Press, 1933, vol 2, p 187. (b) An important paper bearing on the role of phosphocreatine in the activity of the heart (Burns, W, and Cruickshank, E W H. Changes in Creatine, Phosphagen and Adenylpyrophosphate in Relation to the Gaseous Metabolism of the Heart, *J Physiol* **91** 314 [Dec 14] 1937) appeared while the proof on the present article was being read. Burns and Cruickshank investigated the relation between phosphagen (phosphocreatine) and adenylpyrophosphate in the mammalian heart and found that in the excised heart of the cat arrested in certain stages of asphyxia loss of phosphagen preceded that of adenylpyrophosphate and in complete asphyxia the loss was approximately 80 and 60 per cent, respectively, for phosphagen and adenylpyrophosphate. Similar results were obtained with the dog's heart. Fatigue in the presence of oxygen, on the other hand, produced no great loss of phosphagen, although the loss of adenylpyrophosphate was considerably more than that of phosphagen, the loss in the ventricle being 25 per cent for phosphagen and 50 per cent for adenylpyrophosphate.

2 Needham, D M. *The Biochemistry of Muscle*, London, Methuen & Co, Ltd, 1932

3 Fiske, C H, and Subbarow, Y. Phosphocreatine, *J Biol Chem* **81** 629, 1929

Various but unfruitful attempts have been made to ascribe to creatine functions other than its role in muscular contraction. Since creatine is universally present in high concentration in muscle of vertebrates, it is logical to assume that it is an important constituent. Its concentration apparently depends somewhat on the function and efficiency of the muscle⁴ since voluntary muscle contains the highest and smooth muscle the lowest concentration and in certain species white muscle contains more creatine than red muscle.

Although there are many reports on variations in the creatine content of muscles of animals,⁴ a surprisingly small number of observations have been reported on the creatine content of skeletal and cardiac muscles of the human subject.

The first analyses of normal and pathologic human skeletal muscle were made by Chisolm⁵ in 1912 but in the light of more recent data his creatine values were too low, presumably because of the method used or possibly because of postmortem factors. One year later Myers and Fine⁶ reported three creatine analyses of human leg and abdominal muscles. In 1914 Shaffer⁷ found a somewhat decreased creatine content of muscle in 2 patients with diabetes and in 1 patient who died of exophthalmic goiter and in whom muscular efficiency was lowered. Dews⁸ in 1916 confirmed and extended these findings by making determinations of the creatine content of the psoas muscles of 5 normal persons and 70 patients dying of acute and chronic diseases. She found that for most patients dying of acute diseases the muscle gave normal figures for creatine and that for others particularly those dying of septicemia, there was a marked reduction in the creatine content. For those patients who had been in a cachectic condition for several weeks or months before death and who were greatly emaciated, the creatine content of the muscles was reduced both absolutely and relatively, but for the others the creatine value was not decreased.

For 1 patient with generalized myositis fibrosa a disease involving the muscular system Bodansky, Schwab and Brindley⁹ reported a low creatine content, which varied from 160 to 324 mg per hundred grams

4 Hunter, A. Creatine and Creatinine, New York, Longmans, Green & Company, 1928.

5 Chisolm, R. A. The Creatine Content of Muscle in Malignant Disease and Other Pathological Conditions, *Biochem J* **6** 243, 1912.

6 Myers, V. C., and Fine, M. S. The Creatine Content of Muscle Under Normal Conditions. Its Relation to the Urinary Creatinine, *J Biol Chem* **14** 9, 1913.

7 Shaffer, P. A. Observations on Creatine and Creatinine, *J Biol Chem* **18** 525, 1914.

8 Dews, W. Creatine in Human Muscle, *J Biol Chem* **26** 379, 1916.

9 Bodansky, M., Schwab, E. H., and Brindley, P. Creatine Metabolism in a Case of Generalized Myositis Fibrosa, *J Biol Chem* **85** 307, 1929-1930.

of muscle, in 9 different muscles. They found that in this disease there is an inability to retain exogenous creatine, and they suggested that the inflammation interferes with the normal storage of creatine. Bodansky¹⁰ presented analyses of various muscles of 3 normal persons who had died as the result of accidents and showed that the creatine concentration of the pectoralis major muscle, for example, varied from 433 to 484 mg. A severe disturbance of creatine metabolism was observed by Steinitz and Steinfeld¹¹ in a patient with dermatomyositis who was investigated for a considerable period. The individual muscles showed a lowered creatine content, which the authors claimed was referable to anatomic changes in the musculature.

The first figures on the creatine content of human cardiac muscle were reported by Constabel,¹² who gave a range of 170 to 180 mg for normal persons and 70 to 188 mg for patients with pathologic conditions. In Bodansky's¹⁰ 3 normal persons the creatine concentration presumably of the muscle of the left ventricle, varied from 220 to 285 mg. In 1929 Vollmer¹³ found a concentration of 143 mg of creatine in the cardiac muscle of an old man who had fatty degeneration of the heart. Cowan¹⁴ reported a normal range, from 117 to 264 mg, of creatine (comparable creatine, based on an 80 per cent water content) for the left ventricle of 48 supposedly normal persons, the arithmetical mean being 194 ± 33 mg. He stated that this group included persons who showed no clinical symptoms or marked gross or microscopic anatomic changes but that in many cases the heart could not be considered perfectly normal from an anatomic point of view. In 17 patients with heart failure he found the average creatine content of the left ventricle to be 144 mg, which was 50 mg (25.8 per cent lower) than that for his group of normal persons, but the cardiac creatine content of 6 of these patients fell within the normal range. The range for comparable creatine in his group of patients with miscellaneous disorders was from 68 to 208 mg, with a mean of 165 ± 30 mg. He found that septicemia did not reduce the creatine content, and the effect of hypertrophy was not definitely established, although there is a possibility that the hypertrophied heart has a higher creatine content than the nonhypertrophied

10 Bodansky, M. Creatine in Human Muscle, *J Biol Chem* **91** 147, 1931

11 Steinitz, H., and Steinfeld, F. Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, *Ztschr f d ges exper Med* **79** 319, 1931

12 Constabel, F. Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszustanden, *Biochem Ztschr* **122** 152, 1921

13 Vollmer, H. Untersuchungen uber den Kreatin- und Phosphorsaeuregehalt verschiedener Herzteile, *Ztschr f d ges exper Med* **65** 522, 1929

14 Cowan, D. W. The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, *Am Heart J* **9** 378, 1934

heart Recently, Herrmann and his co-workers¹⁵ found that the creatine content of the cardiac muscle varied from 85 to 132 mg, averaging 111 mg, in 13 patients who died of congestive heart failure, from 110 to 137 mg, averaging 123 mg, in 10 patients with chronic syphilitic aortic disease, and from 105 to 205 mg in 32 patients with miscellaneous disorders Hermann Decherd and Oliver stated "The results of our studies, and those of others, convince us that low human myocardial creatine values are more or less constant accompaniments of congestive failure and must be among the significant chemical changes that are associated with myocardial damage and insufficiency Particularly significant are the extremely low total creatine contents of the myocardium from the infarcted areas in cases of coronary thrombosis" Their observations corroborate Cowan's finding of a low cardiac creatine content for patients with congestive heart failure

Still more recently, and since our paper was completed and prepared for publication, Bodansky and Pilcher¹⁶ have reported observations on 310 human hearts (212 males and 88 females) For the males the average creatine content of the muscle of the left ventricle was 157 mg and for the females 163 mg The general deductions which they have drawn from their data are in harmony with our interpretations, although their average findings are considerably lower than those reported by Cowan and by us It appears that their averages were lower largely because of the fact that about 20 per cent of their figures were lower than any figures we encountered in the present and also in a later series Bodansky's earlier findings¹⁰ for the normal myocardium ranged from 220 to 285 mg

Since dissociation of phosphocreatine results from slight injury to tissue incident to the most careful removal from the body and since its splitting is affected by p_H changes,³ occlusion of the circulation, electric tetanization, fatigue and rapid decomposition occurring after death, determinations of the phosphocreatine content are impossible in human beings except in rare instances when biopsies or similar studies are made For this reason estimations of the creatine content were made only for cardiac and voluntary muscle in this series

15 Herrmann, G, Decherd, G M, and Schwab, E H Some Biochemical Factors of Heart Failure, *South M J* **29** 386, 1936 Herrmann, G A Possible Biochemical Basis of Myocardial Failure, in *Medical Papers Dedicated to Henry A Christian*, Baltimore, Waverly Press, Inc, 1936, pp 17-32, *Insuficiencia cardiaca en terminos bioquimicos*, *Arch latino am de cardiol y hemat* **6** 49, 1936 Herrmann, J, Decherd, G, and Oliver, T Creatine Changes in Heart Muscle Under Various Clinical Conditions, *Am Heart J* **12** 689, 1936

16 Bodansky, M, Pilcher, J F, and Duff, V B Clinical Significance of the Creatine Reserve of the Human Heart, *Arch Int Med* **59** 232 (Feb) 1937

Although voluntary¹⁷ and cardiac muscles are distinctly different in structure and function, the voluntary muscle of normal persons has a relatively constant creatine content, the same is probably true of cardiac muscle. From this standpoint it is interesting to determine whether the ratio of creatine in these types of muscle remains constant in various disease conditions. Therefore an attempt has been made in this paper (a) to compare variations in the creatine content of the heart with those of the pectoralis major muscle of patients dying of various diseases and (b) to interpret, if possible, some of the high and low creatine values found for cardiac and voluntary muscles.

EXPERIMENTAL METHOD

Estimation of Creatine in Muscle—The method we employed for the estimation of the creatine content of muscle was described in a previous paper¹⁸. At the time it was stated to be a slight modification of the method of Rose, Helmer and Chanutin. Although that statement is true, the method as modified differs little from the one introduced by Folin in 1914. Folin pointed out at that time that it is possible with the aid of an autoclave to hydrolyze the creatine of a small sample of muscle without extraction. (The autoclave was first employed to convert creatine to creatinine by one of us [V C M] in 1907). Rose, Helmer and Chanutin reduced the amount of muscle tissue used in the Folin method to about 1 Gm and combined this with the Folin-Wu procedure for the estimation of creatine in blood. Since we had difficulty in securing perfectly clear filtrates from cardiac muscle when tungstic acid was used as a clarifying agent, we employed trinitrophenol for this purpose, as well as for the development of the Jaffe color reaction. In other words, the protein precipitable with trinitrophenol was filtered off before the development of color. The method used was, with this slight modification, the method of Folin, incorporating the refinements in technic introduced by Rose, Helmer and Chanutin.

STUDIES ON THE DOG

In a previous communication¹⁸ we reported that the muscle of the left ventricle contains a higher creatine content than that of the right ventricle in the calf, the beef and the lamb as well as in human beings. The findings for 33 dog hearts bear out the same observation. The absolute creatine values for the left ventricle of the dogs ranged from 263 to 355 mg per hundred grams of muscle, averaging 314 mg, and for the right ventricle the creatine concentration varied from 248 to 333 mg, averaging 291 mg. The data are presented in table 1, arranged according to cardiac weight. From an examination of the table it will be evident that there is no exact correlation with cardiac weight. However if the average for dogs 1 to 10 is compared with the average for

17 Myers, V C. Creatine and Creatinine, Yale J Biol & Med 4 467, 1932

18 Seecof, D P, Linegar, C R, and Myers, V C. The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, Arch Int Med 53 574 (April) 1934

dogs 24 to 33, it is found that the larger hearts had a creatine concentration that was about 5 per cent higher. It will be noted that like the ox,¹⁸ the dog has about one-third higher concentration of creatine in the left ventricle than has the human being, namely, 314 mg, in comparison with 208 mg (table 9). The percentage of difference in the creatine content of the respective ventricles was calculated by dividing the absolute difference in milligrams between the creatine contents of the two ventricles by the concentration in the muscle of the left ventricle.

TABLE 1—*Creatine Content of Muscles of Left and Right Ventricles of Normal Dogs, Arranged According to Cardiac Weight*

Dog	Cardiac Weight, Gm	Creatine Content, Mg per 100 Gm of Muscle		Difference Between Left and Right Ventricle	
		Left Ventricle	Right Ventricle	Mg	%
1	225	28	305	2	7.0
2	185	308	271	37	11.0
3	160	331	295	36	10.9
4	155	327	311	16	4.9
5	140	291	281	10	3.4
6	127	317	307	10	3.2
7	120	316	26	20	5.8
8	115	321	207	24	7.5
9	111	334	06	28	8.4
10	114	328	302	26	7.9
11	113	314	320	24	7.0
12	111	303	295	8	2.6
13	112	303	290	13	4.3
14	110	277	236	21	7.6
15	106	309	293	16	5.2
16	99	311	118	2	6.7
17	98	355	290	65	18.3
18	95	309	276	33	10.7
19	95	284	272	12	4.2
20	90	275	258	17	6.2
21	89	348	133	15	4.3
22	85	318	258	60	18.9
23	84	319	307	12	3.8
24	83	306	291	15	4.0
25	80	293	265	28	9.6
26	75	340	305	35	9.4
27	71	263	218	45	15.7
28	71	301	285	16	5.3
29	70	319	281	38	11.9
30	69	326	299	27	8.3
31	67	297	285	12	4.0
32	65	322	307	15	4.7
33	57	315	263	52	16.5
Average		314	291	23	7.3

The differences ranged from 6 to 65 mg, or from 2.6 to 18.9 per cent with an average of 23 mg, or 7.3 per cent. The finding of a higher creatine concentration in the left ventricle supports our earlier observations on the hearts of man and of the ox, although it must be noted that the difference between the ventricles of the dog is much smaller. The average difference for 95 human hearts was 28.4 per cent and for 6 beef hearts 12.6 per cent, in comparison with 7.3 per cent for the dog. Compared with the human heart, this higher creatine concentration in the heart of the dog, together with the smaller difference between the ventricles, is obviously a fact of considerable significance from the

standpoint of comparative physiology, which will not be discussed further at this time

Perfusion experiments on dog hearts *in vivo* showed that creatine can be removed from cardiac muscle. In these experiments a cannula pointing peripherally was inserted into the descending branch of the left coronary artery, the central end of the descending branch being ligated. The beating heart was then perfused through this cannula with aerated Locke's solution. By this procedure practically the only part perfused was the anterolateral and apical portion of the left ventricle. The remaining part of the left ventricle and practically the entire right ventricle received a normal blood supply through the circumflex branch of the left and right coronary arteries, respectively.

Area 1 in table 2 refers to the portion of the ventricle just peripheral to the point of introduction of the cannula, where the perfusion was greatest, area 2 refers to the apex of the left ventricle, where the

TABLE 2—*Effect of Perfusion of Left Coronary Artery on Creatine Content of Cardiac Muscle in Dogs*

Dog	Creatine Content, Mg per 100 Gm of Muscle				Cardiac Weight, Gm	Volume of Perfusion Fluid, Liters	Comments on Perfusion
	Left Ventricle			Right Ventricle			
	Area 1	Area 2	Area 3				
1	340	331		344	210		Unsuccessful
2	189	210		282	118	1.6	Successful
3	216	232	283*	304	175	3	Successful
4	180	325		326	125	3.4	Successful
5	183		340	311	125	2.3	Successful

* Area 3 was visibly perfused

perfusion was less pronounced, and area 3 refers to the nonperfused or least perfused section on the posterior portion of the left ventricle. Consequently, as is shown in the table, creatine values were reduced more for area 1 than for other parts of the ventricle. The right ventricle was not perfused and was therefore used as a control, because the left ventricle was found to have a higher creatine content normally. In each case the perfusion was carried on until fibrillation began in the ventricles. This occurred in one instance in ten minutes (dog 1) and in another after as long as four hours (dog 5).

It is obvious that even a short perfusion of ten minutes' duration removed some creatine, because the values for the right ventricle were found to be higher than those for the left. There was a marked reduction in the creatine concentration of the perfused portion of the left ventricle in the experiments (dogs 2 to 5) which were continued for from one hundred to two hundred and forty minutes before fibrillation ensued. Perfusions of greater duration, *viz.*, two hundred and forty minutes, and with greater volumes of perfusate did not remove more

creatine than those performed in the one hundred minute period, but this may have been due to better perfusion in the latter experiments or may have been incident to variable degrees of phosphocreatine dissociation¹⁹

STUDIES ON HUMAN MATERIAL

All the human material was obtained immediately after death, and no discrimination was used in its selection. As a result, various types of conditions are included in this series, and only the 95 cases which were analyzed within twenty hours post mortem are included (with the exception of 1 case of lobal pneumonia [case 26], 1 each of acute and chronic infection, the cases of young patients and 4 cases of miscellaneous conditions, these being analyzed within thirty-six hours). In each case the creatine content of both ventricles of the heart and in most cases of the pectoralis major muscle was determined. The creatine concentration for both the cardiac and the voluntary muscle is expressed in milligrams per hundred grams of muscle.

In some of the cases to be presented many different clinical and pathologic diagnoses were made, so that it was difficult to segregate the cases into groups entirely on the basis of one uncomplicated condition. It was likewise difficult to separate such a miscellaneous lot of cases into groups in which the creatine content of either the cardiac or the voluntary muscle or both underwent certain definite changes, because of the lack of knowledge regarding all the functions and the origin of creatine and the reason for variations in the concentration of this constituent in the muscles. From the data on muscle creatine in the literature¹ it is apparent that (a) the creatine content of voluntary muscle may be reduced in muscular weakness, (b) it is primarily increased during fasting, after which it may decrease, (c) it is increased in other conditions associated with loss of weight (such as phosphorus poisoning and experimental scurvy) and (d) it tends to be lowered in chronic diseases, but may or may not be reduced in acute conditions (the value for cardiac creatine²⁰ is reduced in congestive heart failure).

Grouping the cases on a somewhat similar basis seemed to be a logical procedure to follow. Therefore, the following major groupings of the cases in which the diagnoses were definitely established appeared to give the most logical presentation of the data. The remainder of the cases which did not fall into one of these major classes were placed in a group of miscellaneous cases, mainly because each diagnosis was

¹⁹ Dr. C. J. Wiggers turned over to us these 5 hearts after the perfusion experiments noted.

²⁰ Linegar, C. R., and Myers, V. C. Further Studies on the Creatine Content of Heart Muscle, *Proc. Soc. Exper. Biol. & Med.* **32**: 1016, 1935. Cowan¹⁴ Herrmann, Decherd and Schwab¹⁵

complicated and the cause of death was questionable or could not be attributed primarily to one disease process or because the cases could not be placed in other groups

Normal Values—At present it does not appear that normal creatine values have been established for either the voluntary or the cardiac muscle of the human subject, although Bodansky¹⁰ has reported analyses of various voluntary muscles of 3 subjects who died by accident. His figures for the pectoralis major muscle, as already stated, varied from 433 to 484 mg per hundred grams of muscle. These figures are considerably higher than those hitherto reported, and until they are confirmed by additional figures it seems best to compare our figures for voluntary muscle with the average for the present data and other unpublished analyses, namely, about 400 mg. The average creatine content of cardiac muscle in this series was 208 mg for the

TABLE 3—*Creatine Content of Cardiac Muscle in Lobal Pneumonia*

Serial No	Age, Yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %		
45	75	M	263	150	43.0	475	472
24	29	M	247	181	26.7	400	427
111	47	M	233	173	25.8	350	397
43	61	M	227	130	42.7	300	383
26	22	M	216	130	39.8	271	428
Average			237	153	35.4		441

left ventricle and 149 mg for the right. On the basis of these and other analyses, we have tentatively considered the normal content of creatine in the muscle of the left ventricle to be about 200 mg and that in the right ventricle 150 mg.

Lobal Pneumonia—The values for the creatine content of cardiac and voluntary muscles in lobal pneumonia are given in table 3. Although these values are close to those given by Bodansky¹⁰ for 3 normal persons, it seems doubtful whether muscles of patients with lobal pneumonia can be considered normal, because of the fever and possible nitrogen retention. One patient (case 45) for whom the creatine content of the cardiac and voluntary muscles was in the higher range for this series showed no creatinine retention, and for the others determinations of the creatinine content of the blood were not made. The solid contents of the cardiac and voluntary muscles in cases 45, 111 and 43 were found to vary only slightly from the averages previously reported¹⁸. As will be noted, the creatine content of both the voluntary and the cardiac muscle was reasonably constant in these 5 cases of lobal pneumonia, but the values for the left ventricle and voluntary muscle were considerably above the average values.

In the group of patients with miscellaneous conditions, the data for which are given in table 9, are included 8 patients with bronchopneumonia and 3 with lobal pneumonia for whom pneumonia was not considered the major pathologic diagnosis. The creatine content of the muscle of the left ventricle of the patients with bronchopneumonia ranged from 219 to 259 mg, and averaged 238 mg, figures comparable with those for the patients with lobal pneumonia, given in table 3. The findings for the 3 patients with lobal pneumonia, however, were much lower than those given in table 3, namely from 145 to 188 mg, with an average of 174 mg for the muscle of the left ventricle.

Cardiac Decompensation—As may be observed in table 4, the creatine content of cardiac muscle is uniformly lowered in heart failure.

TABLE 4—Creatine Content of Cardiac and Pectoralis Major Muscle in Cardiac Decompensation

Serial No	Age, Yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %		
103	33	M	220	144	34.5	250	433
35	26	F	194	146	25.0	375	346
97	50	M	192	178	7.3	730	348
50	46	F	187	125	33.2	300	387
15	62	M	183	120	34.4	750	
116	47	M	178	111	37.6	760	318
17	77	M	163	127	22.1	375	
86	76	M	162	153	5.6	400	497
65	58	M	160	124	22.6	450	
60	60	F	146	109	25.3	825	
38	43	M	138	114	17.4	275	367
Average			175	132	24.6		390

In all these cases the diagnosis was made clinically as being primarily cardiac decompensation, although the first case is one of acute circulatory collapse and secondary anemia following malaria treatment for tertiary syphilis and the creatine content of the muscle was similar to that in lobal pneumonia.

In 5 of the cases listed in table 4 the solid content was determined and found to be similar to that in cases of lobal pneumonia. This confirms the work of Cowan²¹ and Calhoun and his co-workers,²¹ who found that the water content of cardiac muscle of subjects dying of heart failure was not significantly altered, and eliminates variation in water content as a possible cause of the decreased creatine content. Cowan also stated that fibrous tissue contains less creatine than muscular tissue, but this factor was negligible in his series of cases. A study of variations in the fibrous tissue of the decompensated heart was not made in this series.

21 Calhoun, J. A., Cullen, G. E., Clarke, G., and Harrison, T. R. Studies in Congestive Heart Failure. VI. The Effect of Overwork and Other Factors on the Potassium Content of Cardiac Muscle, *J. Clin. Investigation* 9:393, 1930.

The creatine content of voluntary muscle was decreased slightly in all except cases 86 and 103, and the diminution bore no relation to the variations in cardiac muscle

Diabetes—For the 4 patients with diabetes, listed in table 5, the creatine content of the voluntary muscle was markedly reduced. In 2 of these cases the values for cardiac creatine were lowered as well, in

TABLE 5—Creatine Content of Cardiac and Pectoralis Major Muscle in Diabetes

Serial No	Age, yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg	Carbon Dioxide Capacity of Blood, Vol %
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %			
99	67	F	275	152*	44.7	350	308	
34	58	F	195	156	20.0	350	324	20 to 29
29	43	F	158	120	24.1	275	282	15
31	68	M	152	144†	5.3	500	339	
Average			195	143	26.7		313	

* Slightly fatty

† Greatly hypertrophied

1 case there was slight diminution and in the remaining case the creatine value was even higher than the value in lobar pneumonia. Again there was a lack of correlation between the variations in the creatine content of cardiac and voluntary muscle. In cases 34 and 29 the carbon dioxide capacity of the blood was from 20 to 29 and 15 volumes per cent, respectively, indicating a markedly reduced alkali reserve.

TABLE 6—Creatine Content of Cardiac and Pectoralis Major Muscle in Carcinoma

Serial No	Age, yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %		
94	45	M	255	179	29.8	300	
68	52	M	192	167	13.0	300	347
51	58	M	174	135	22.4	250	
32	23	M	170	120	29.4	275	310*
113	60	M	170	118	30.6	500	364
61	52	F	116	112	3.4	350	
Average			180	129	35.3		340

* Osteosarcoma of right humerus. The right pectoralis major muscle showed 87 mg of creatine, the left, 310 mg.

Carcinoma—The cases listed in table 6 include those of carcinoma of the left lung, of the left cervical lymph nodes and of the esophagus, osteosarcoma of the right humerus, carcinoma of the tail of the pancreas and annular carcinoma of the transverse colon, listed in the order given in the table. In these cases there was a lowered creatine content of voluntary muscle and with the exception of the first case there was always a lowered creatine concentration in the cardiac muscle.

Acute and Chronic Infections—In comparison with the average creatine value, only 3 of the 15 patients with acute infection showed a lowered creatine content of cardiac muscle, namely 2 with septicemia and 1 with gangrene following prostatectomy, whereas 5 of the patients (encephalitis, encephalosis, meningitis, erysipelas and peritonitis) showed an elevated value for cardiac creatine. The rest of the patients showed a normal value for cardiac creatine. The creatine content of the voluntary muscle was lowered for 2 of 3 patients with septicemia, for 1 patient with peritonitis and for both patients with meningitis, i. e., in 5 of the 9 patients for whom estimations were made.

Half the 14 patients with chronic infection or tuberculosis had a lowered and 5 had an increased value for cardiac creatine, as compared with the average, whereas 5 of the 8 values for the creatine content of voluntary muscle were reduced.

TABLE 7—*Creatine Content of Cardiac and Pectoralis Major Muscle in Uremia with Heart Failure*

Serial No	Age, Yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg	Blood Creatinine, Mg	Carbon Dioxide Capacity of Blood, Vol %
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %				
82	49	F	207	163	21.3	400	376	3.3	
123	39	M	194	136	29.9	600	360	10.0	38
114	33	F	190	140	26.3	650		2.5	
124	46	M	161	140	13.1	900	418	6.2	42.27
119	57	M	152	123	19.1	960	449	22.0	10
122	47	F	144	116	19.5	450		21.0*	6*
Average			176	136	22.3		401		

* Blood obtained post mortem

Uremia and Uremia Plus Cardiac Decompensation—When all the values for blood creatinine were placed in tabular form in descending order, it was found that neither the creatine content of voluntary nor that of cardiac muscle bore any relation to creatinine retention. However, by further analysis it was apparent that in most of the patients for whom the creatine content of the cardiac muscle was low, heart failure was a complication. On this account it seemed advantageous to rearrange the data on a different basis, with regard to uremia and uremia associated with heart failure.

In the patients with uremia plus heart failure (listed in table 7) the creatine content of the cardiac muscle bore no relation to the creatinine retention. The first patient had acute heart failure due to coronary thrombosis, with no reduction in the creatine content of the cardiac muscle, but the remainder of the values for cardiac creatine were low, like those for patients with cardiac decompensation (table 4). Two of 4 patients showed a low value for the creatine content of the voluntary

muscle The last 2 patients showed a marked reduction in the carbon dioxide capacity of the blood

On the other hand, the patients with uremia uncomplicated with heart failure (listed in table 8) tended to show a high value for creatine in both cardiac and voluntary muscle, although there did not appear to be any relation to creatinine retention or to the carbon dioxide capacity of the blood Unfortunately, a determination of the creatinine content of the blood was not made in case 115, but the clinical and anatomic findings indicated severe uremia There appeared to be no other explanation for the high creatine values in cases 18 and possibly 115 than that marked retention of creatine had a mass effect on the creatine-creatinine equilibrium

Young Human Beings—All the young human beings except the asphyxiated new-born infant died of acute infections There is essentially no difference in the creatine content of the ventricular muscles

TABLE 8—*Creatine Content of Cardiac and Pectoralis Major Muscle in Uremia*

Serial No	Age, Yr	Sex	Creatine Content			Cardiac Weight, Gm	Creatine of Pectoralis Major Muscle, Mg	Blood Creatinine, Mg	Carbon Dioxide Capacity of Blood, Vol %
			Left Ventricle, Mg	Right Ventricle, Mg	Difference, %				
18	60	M	369	283	23.3	500	520	25.1	38
115	60	F	348	138	54.6	150	561		
105	4	M	251	209	17.7	300	197	5.1	
120	17	M	249	201	18.1	525		17.8	21
121	73	M	216	196	13.9	500	48	5.8	17
Average			287	210	26.8		501		

of the new-born, and for all the other patients, ranging from 1 month to 4 years of age, the creatine content of the left ventricle was higher than that of the right The value for cardiac creatine is low at birth and gradually increases to the value for adults within the first year At the same time, the percentage of difference in the values for creatine in the two ventricles gradually increases, showing that the creatine content of the left ventricle increases more rapidly than that of the right and that the augmentation of the creatine concentration in the right ventricle is comparatively small This fact may be correlated with the amount of work the two ventricles perform in the growing infant For some unexplained reason, one patient, a child of 3 months who died of lobar pneumonia, pertussis and varicella, showed a creatine value for the left ventricle which corresponded to an extremely low value for the right ventricle Furthermore, the weight of the heart of this infant was about twice that of others at this age period With omission of this case, it is also apparent that creatine values similar to those for adults are reached in cardiac muscle at about 4 months of age, which is many months before saturation of the voluntary muscle

with creatine takes place. This is also shown by the observations of Vollmei,¹³ but not by those of Beker²² for other species.

Miscellaneous Conditions—This group includes cases in which the primary cause of death was questionable or which did not fit into any other group. There were cases of leukemia, hepatic insufficiency, thyrotoxicosis, syphilis, intestinal obstruction, hemachromatosis and pellagra and cases in which the cause of death was not definite. The patient with leukemia showed a cardiac creatine content in the upper range for those with uremia and a voluntary creatine concentration definitely above the average normal value. Compared with the average, the patients with hepatic insufficiency showed an increased creatine content of voluntary and cardiac muscle, whereas 1 patient with cirrhosis and 1 with thyrotoxicosis showed a slightly lowered content in the

TABLE 9—Summary of Average Data on Creatine Content of Cardiac and Pectoralis Major Muscle

No. of Cases	Creatine Content			Creatine of Pectoralis Major Muscle, Mg	Grouping
	Left Ventricle, Mg	Right Ventricle, Mg	Difference, %		
7	287	210	26.8	501	Uremia
5	237	173	35.4	141	Lobar pneumonia
17	223	171	32.1	191	Acute infections
20	208	148	28.8	112	Miscellaneous
9*	206	178	21.1	328	Young human beings
14	206	178	28.2	382	Chronic infections
4	197	141	26.7	313	Diabetes
6	180	129	37.1	340	Carcinoma
6	176	116	22.3	101	Uremia with heart failure
11	175	132	24.6	190	Cardiac decompensation
Total and averages	97	208	119	28.4	505

* Average age, 1 year

cardiac muscle and an increased content in the voluntary muscle. Similarly, the patient with pellagra showed markedly decreased creatine values for cardiac and voluntary muscle, the 2 patients with syphilis showed a normal value for cardiac muscle and a lowered value for voluntary muscle and the patient with hemachromatosis and intestinal obstruction showed an increased cardiac concentration. The data for the rest of the patients are of little significance because of the questionable cause of death.

Summary of the Variations in the Creatine Values for Cardiac and Voluntary Muscle—Table 9 presents a summary of the cases according to the adopted schemata, the data being arranged in the descending order of average creatine values for the left ventricle for each group. It shows that the lowest figures for adult voluntary muscle were

22 Beker, J. C. Die Verteilung des Kreatins im Säugetierkörper, *Ztschr. f. physiol. Chem.* **87** 21, 1913.

obtained for patients with diabetes and carcinoma and the highest for those with uremia and lobar pneumonia. The patients with uremia and lobar pneumonia also showed the highest cardiac creatine concentrations encountered, while the lowest were shown by those with heart failure, regardless of whether or not this condition was associated with uremia.

It will be observed from an inspection of table 9 that, despite the fact that the lowest values for the creatine content of cardiac muscle were shown by patients with heart failure, these patients did not show the lowest values for the creatine content of voluntary muscle, the values being close to the average found for the series. Furthermore, the creatine content of cardiac muscle was not markedly lowered for those with diabetes, despite the fact that they showed the lowest values for the creatine content of voluntary muscle. It might be concluded

TABLE 10—*Comparison of Creatine Content of the Pectoralis Major and Cardiac Muscle*

	No of Cases	Pectoralis Major Muscle		Ventricular Muscle		
		Range, Mg	Average, Mg	Average for Left Ventricle, Mg	Average for Right Ventricle, Mg	Difference, %
	11	282-329	307	202	142	26.5
	11	330-363	347	208	160	23.1
	11	354-396	378	198	134	32.3
	11	397-426	410	195	145	32.3
	11	427-451	436	232	164	29.3
	12	452-564	484	258	163	36.8
Total and average	67		395			

from this that there is no relation between the level of the creatine concentration in voluntary and that in cardiac muscle. However, if the data are arranged on the basis of the concentration of creatine in the voluntary muscle, as in table 10, this does not appear to be entirely true. It will be observed that as long as the concentration of creatine in the voluntary muscle did not exceed about 425 mg, the concentration of creatine in the muscle of the left ventricle remained relatively constant, but when the concentration in the voluntary muscle exceeded this level, perhaps the normal saturation level, then there appeared to be a definite rise in the creatine concentration of the left ventricle. This is true of the last two groups of 11 and 12 cases, in which the average creatine content of the voluntary muscle was 436 and 484 mg, respectively. There was also some increase in the creatine concentration in the right ventricle, but the increase in the left ventricle was considerably larger, particularly in the last group of 12 cases.

COMMENT

It is highly improbable that one would find in any such indiscriminately chosen series of patients who died of acute and chronic infections, heart failure, uremia, diabetes, cancer and other disease conditions many who would show a normal concentration of muscle creatine. Strictly speaking, the cardiac and voluntary muscles cannot be considered normal except when the person is healthy and robust and meets death other than by way of disease.

Since there were no normal persons in this series and, furthermore, since there are insufficient data in the literature on which to define the normal values for the creatine content of voluntary and cardiac muscle, it appears that the only procedure to be followed at present is to take the average figures given in table 9 as the basis for comparison.

Although it is possible that the normal creatine content of human voluntary muscle is slightly in excess of the average given, namely, 395 mg, we doubt that the average normal content exceeds this figure by more than from 5 to 10 per cent. In a more recent unpublished study carried out in this laboratory on the same muscle (*pectoralis major*) Mangun obtained an average of 400 mg for 34 persons. In another study in our laboratory Corsaro²³ obtained averages of 405, 402 and 388 mg, respectively, for the *psoas major*, *rectus abdominis* and *sternocleidomastoid* muscles in 74 cases. Thus it appears that the creatine concentration of human voluntary muscle obtained at autopsy is close to 400 mg. Since the number of figures both above and below this average in Corsaro's series about balanced each other, this figure may possess some importance. It is also significant, as will be noted in table 10, that as long as the creatine concentration of voluntary muscle does not exceed 425 mg, the average creatine concentration in the muscle of the left ventricle remains relatively constant, but when the creatine concentration of voluntary muscle exceeds this level there is also a rise in the creatine concentration of the cardiac muscle, suggesting that the normal saturation level of the voluntary muscle has perhaps been exceeded.

In the case of human cardiac muscle it is still more difficult to define the normal. However, one might assume that since the heart performs a less variable amount of work than voluntary muscle, its creatine concentration should remain relatively constant. In the present series of cases the creatine concentration of the cardiac muscle was found to be 208 mg per hundred grams of tissue for the left ventricle and 149 mg for the right ventricle. Partly on the basis of the distribution of the values, we are inclined to believe that our average figures are not far

²³ Corsaro, J. F. The Creatine Content of Human Voluntary Muscle, *Proc Soc Exper Biol & Med* **35** 554, 1937.

from the normal creatine concentration. In a recent unpublished study Mangun obtained average creatine values of 199 mg for the muscle of the left ventricle and 153 mg for that of the right ventricle in 69 cases, the value for the left ventricle being about 4 per cent lower and that for the right ventricle about 3 per cent higher than in the present series. The average for both series is 204 mg for the left ventricle and 151 mg for the right ventricle, or, in round numbers, 200 mg for the left and 150 mg for the right ventricle.

In heart failure the creatine content of the muscles of both ventricles is uniformly lowered in cardiac decompensation except in acute conditions, such as coronary thrombosis. In some of these cases the creatine value seems to be lowered more for the left ventricle than for the right, as is shown by the small percentage of difference between the creatine values, which is suggestive of a tendency toward failure of the left side of the heart. We had hoped to find cases in which the creatine content of the muscle of the left ventricle would actually be lower than that of the right, to bear this contention out more definitely, but we were unable to do so. Conversely, any large percentage of difference in the creatine content of the two ventricles might be taken as an indication of failure of the right side of the heart. As a matter of fact the figures in some of the cases suggest a tendency in this direction, but the data are not conclusive. Therefore, on the basis of the cases presented here it appears that when the heart becomes decompensated it fails as a unit and not in a separate portion, such as in one ventricle, and that if the creatine content of one ventricle is lowered because of heart failure the creatine concentration of the other ventricle also falls. A more extensive series in which there was a larger percentage of difference and in which the left ventricle had a lower creatine content than the right might support the contention of the failure of the muscle of the left or right ventricle.

The fact that creatine can be washed out of cardiac muscle by perfusion indicates that part of it is present in a diffusible form. It has been shown that the diffusion of phosphoric acid²⁴ or creatine²⁵ is greater in fatigued than in resting muscle. This fact correlates with the greater dissociation of phosphocreatine under the same conditions.³ Since the bound form of creatine is not diffusible, the source of the increased amounts of diffusible creatine must be the decomposition of phosphocreatine. It may be that the low creatine value for the fatigued heart (cardiac decompensation) is due to the greater breakdown of

24 Stella, G. The Concentration and Diffusion of Inorganic Phosphate in Living Muscle, *J. Physiol.* **66** 19, 1928.

25 Tieg, O. W. Function of Creatine in Muscular Contraction, *Australian J. Exper. Biol. & M. Sc.* **2** 1 1925. Eggleston, P. The Diffusion of Creatine and Urea Through Muscle, *J. Physiol.* **70** 294, 1930.

phosphocreatine into a diffusible form or to inadequate resynthesis of phosphocreatine due to faulty nutrition of the heart and that the creatine thus released diffuses out of the muscle into the blood stream (The recent work of Burns and Cruickshank^{1b} is in harmony with this view) Nevertheless, a low creatine content in cardiac muscle and heart failure are definitely related It is now known that a low creatine value is associated with weakness of voluntary muscles, and it may be concluded that a low cardiac creatine content in heart failure and possibly in other conditions is connected in some way with the weakness of the cardiac muscle, but whether the lowering of creatine causes, contributes to or merely results from this condition remains to be determined

Heimann and his colleagues¹⁵ suggested that in myocardial failure either suboxidation or anoxemia is present which causes an inadequate removal of lactic acid and that this product accumulates in the cardiac tissue The lower p_H value results in increased hydrolysis of phosphocreatine and interferes with its resynthesis, and this may well hold its concentration at a low level and thus contribute to myocardial weakness

In a study of variations in the potassium content in congestive heart failure Calhoun and his associates²¹ concluded that cardiac fatigue and failure are due to loss of potassium from cardiac muscle and that this loss is the predisposing factor It is well known that a certain balance of electrolytes, of which potassium, sodium and calcium are the most important cations, is necessary in living, functioning tissues A marked disturbance of the osmotic equilibrium affects the physiologic functions of these tissues, as may be demonstrated, for example, by perfusion of the heart with potassium-excessive and potassium-deficient Ringer's solution Consequently, potassium as well as the other cations cannot be overlooked in a chemical study of heart failure Furthermore, it is probable that decreases of both potassium and creatine are associated in the failing heart, and since potassium,²⁶ creatine¹⁸ and phosphorus^{26a} show a higher content in the left ventricle than in the right, this fact indicates that creatine phosphoric acid probably exists as a potassium salt in cardiac muscle as well as in skeletal muscle In a recent preliminary report Mangun and Myers²⁷ have noted that when the heart is hypertrophied there is a decrease in the concentration of creatine, potassium and phosphorus, generally somewhat in proportion to the ratios which exist in the dipotassium salt of phosphocreatine

26 (a) Cullen, G E, Wilkins, W E, and Harrison, T R Electrolytes in Human Tissue II The Electrolyte Content of Hearts and Other Tissues from Cases with Various Diseases, *J Biol Chem* **102** 415, 1933 (b) Calhoun and others²¹

27 Mangun, G H, and Myers, V C Creatine, Potassium and Phosphorus Content of Cardiac and Voluntary Muscle, *Proc Soc Exptl Biol & Med* **35** 455, 1936

It may be tentatively assumed that the low creatine values for voluntary muscle in diabetes and for cardiac muscle in heart failure are due to faulty nutrition, which results in incomplete resynthesis of phosphocreatine, with consequent diffusion of creatine from the muscles and creatinuria. The faulty nutrition in diabetes may be traced almost directly to the disturbed carbohydrate metabolism, and in heart failure this might be brought about by overwork or an inadequate blood supply. An explanation of the high creatine values encountered in uremia and pneumonia, on the other hand, is more difficult. It is generally recognized, as a result of experimental work on animals, that there may be a considerable increase in the creatine concentration of voluntary muscle in the early stages of starvation, while in the premonitory stages there may be a marked drop in the muscle creatine. These changes are not due to fluctuations in the water content of the muscle, although the moisture content may have some influence on the creatine concentration. Normal muscle is able to take up and hold temporarily a small amount of creatine when this is administered. Since there is an equilibrium between creatine and creatinine, it is logical to expect that retention of creatinine as a result of renal disease might lead to an increase in the creatine concentration in voluntary and cardiac muscle. This is not invariably true, since in some cases of uremia with creatinine retention there is a low concentration of creatine in both voluntary and cardiac muscle. As already pointed out, it is a singular fact that in these cases heart failure has been manifest, whereas this has not been true in cases in which there was an increased creatine concentration in the cardiac muscle. Long before the discovery of phosphocreatine it was assumed that in some way the urinary creatinine coefficient (and with it the creatine content of muscle) is related to muscular efficiency. It may well be that factors which tend to maintain or raise the creatine content of cardiac muscle tend to retard the failure of ventricular muscle. Creatine and creatinine retention appear to offer the most plausible explanation of the high values encountered in some cases of uremia. Somewhat elevated values for the creatine of both voluntary and cardiac muscle have been encountered in lobar pneumonia and bronchopneumonia. The renal damage seems hardly sufficient here to explain the findings, but it is a well known fact that in cases of fever there is a marked increase in the excretion of creatinine (up to 35 per cent). A definite increase in the creatinine concentration of the blood has also been observed. It is possible that with the increased formation of creatinine in fever there is also an increased formation of creatine and that the renal excretion is unable to keep pace with this increased formation, thus leading to an increased concentration in the muscles. This seems to harmonize with the known facts. It is of interest to note that, in general, when elevation of the

creatine values is present there is a much greater increase in the creatine concentration in the muscle of the left than in that of the right ventricle.

In the foregoing discussion it has been shown that concentrations of creatine in cardiac muscle are increased or normal in lobar pneumonia and uremia and reduced in heart failure. The creatine content of cardiac muscle also is lowered in 50 per cent of the cases of tuberculosis, in 20 per cent of the cases of acute infection, in 83 per cent of the cases of carcinoma and in 75 per cent of the cases of diabetes. Likewise, the creatine value for voluntary muscle is increased or normal in cases of lobar pneumonia and uremia, whereas it is lowered in all cases of diabetes and carcinoma, in 5 of 10 cases of acute infection and in 5 of 8 cases of tuberculosis.

In 7 of 11 cases of cardiac decompensation the creatine concentration of the voluntary muscle is lowered, but not in direct relation to the decrease in the value for cardiac muscle. It is possible that the weakened condition of the heart permits less activity on the part of the patient and that disuse of the voluntary muscle results in atrophy and reduced efficiency. In cases of diabetes and such a condition as carcinoma the creatine value for voluntary muscle is consistently lowered, but the reduction in the creatine concentration in the cardiac muscle is comparatively small. Young human beings show a relatively higher creatine content of cardiac than of voluntary muscle which indicates that the value for cardiac muscle reaches adult levels before that for voluntary muscle. In cases of uremia the creatine values for both cardiac and voluntary muscle tend to be high, and in cases of lobar pneumonia they are either somewhat elevated or about normal.

The bulk of the evidence obtained points to the concept that the variations in the creatine content of cardiac and voluntary muscle are not closely related. In other words, the circulatory and perambulatory systems of the body have individual functions to perform, although these functions are united in a coordinated organism. Although disease of one system has an influence on the other system, it is unlikely to exert more than a slight effect.

SUMMARY AND CONCLUSIONS

The cardiac muscle of the left ventricle of the dog has a higher creatine content than that of the right, which confirms the findings previously reported for other species. In comparison with man, however, the dog has a higher creatine concentration in the muscle of the heart, and the difference between the two ventricles is much smaller.

Perfusion of the heart of a dog *in vivo* with Locke's solution through the descending coronary artery markedly reduces the creatine content of the perfused area.

The creatine content of the heart of an infant is low at birth and progressively increases to adult values within a few months after birth.

The saturation level for the creatine of cardiac muscle is reached much earlier than that for the creatine of voluntary muscle

In comparison with average values, the creatine content of the heart, i. e., of both the left and the right ventricle, is definitely lowered in cardiac decompensation. It is also usually slightly lowered in diabetes and carcinoma. On the other hand, the creatine content of the muscles of the left and right ventricles may be considerably increased in uremia uncomplicated with heart failure and in some cases of pneumonia.

Compared with average values, the creatine content of voluntary muscle (taking the pectoralis major muscle as an example) is reduced in diabetes and carcinoma and increased in uremia uncomplicated with heart failure and in the pneumonias.

The creatine content of cardiac and voluntary muscle may be reduced or increased in fairly constant ratios, but the major evidence points to the conclusion that variations in these two distinctly different muscles are not related, except in the cases in which the creatine content of both voluntary and cardiac muscle is elevated, probably as a result of nitrogen retention.

EFFECT OF JAUNDICE ON CHRONIC INFECTIOUS (ATROPHIC) ARTHRITIS AND ON PRIMARY FIBROSITIS

FURTHER OBSERVATIONS, ATTEMPTS TO REPRODUCE
THE PHENOMENON

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On April 1, 1929, a patient came to the Mayo Clinic complaining of chronic infectious (atrophic rheumatoid) arthritis of four years' duration. He stated that a week previously, no medicine having been taken, painless jaundice suddenly developed. He said that on March 25, the day after he noted the jaundice, the pain and swelling in his joints began to diminish. When the patient was examined at the clinic the joints were symptomless, this complete symptomatic remission lasted five months with respect to the feet and eight months with respect to the hands. The phenomenon so impressed the patient that when he returned to the clinic two years later (May 1931), with moderately active arthritis, he reminded me that the only time his joints ever had been entirely free from pain was during and just after the jaundice. In the meantime, three other patients who had come under my observation had experienced the same phenomenon.

In the next four years I found a total of fourteen patients with "rheumatic" complaints (nine with chronic infectious arthritis, three with primary fibrositis and two with sciatic pain) who had experienced marked and generally complete symptomatic remission with the appearance of jaundice. In all cases the jaundice was of the intrahepatic type, in twelve cases it was due to cinchophen or derivatives of cinchophen, but two patients who had taken no medicine had the "catarrhal type" of intrahepatic jaundice. This indicated that jaundice, not cinchophen, was responsible for the dramatic remissions which lasted for a number of weeks or months, occasionally longer, after which symptoms recurred in most cases.

From the Division of Medicine, the Mayo Clinic

Read before the Fifth Conference on Rheumatic Diseases held by the American Rheumatism Association, Atlantic City, N. J., June 7, 1937

When these observations¹ were first reported I was unable to find any previous references to this phenomenon except three casual statements. With regard to cinchophen toxicity, Parsons and Harding² had noted the case of a woman with "rheumatism" who, after taking "Renton's hydrocin tablets" (containing approximately 5 grains [0.3 Gm.] of cinchophen), had jaundice and died. The writers stated that though the tablets "made her dizzy, the rheumatism disappeared." In a later report on cinchophen toxicity³ they stated "A history of the taking of cinchophen followed by disappearance of pain associated with the onset of jaundice is usually obtained." In another paper on cinchophen toxicity Grigg and Jacobsen⁴ noted the case of a woman with arthritis of many years' duration. Cinchophen caused the development of jaundice, and she died. Without other comment the statement was made "It is worthy of note that after the appearance of the jaundice she had no subjective symptoms of arthritis." Since then another brief passing comment has been called to my attention. In his clinical lecture entitled "On a Form of Chronic Joint Disease in Children," Still⁵ (1897) stated "Curiously enough, some accidental complications have been followed by marked improvement, thus I have known measles, scarlet fever, and catarrhal jaundice to be each followed by distinct improvement of the joint symptoms."

Since the publication of my first report, Sidel and Abrams⁶ and Borman⁷ have made confirmatory observations.

1 Hench, P. S. Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis, and Sciatic Pain, *Proc. Staff Meet., Mayo Clin.* **8** 430-436 (July 12) 1933, Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, *J. A. M. A.* **101** 1265-1266 (Oct. 14) 1933, The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis, and Sciatic Pain, *Ann. Int. Med.* **7** 1278-1294 (April) 1934. These observations were reported at the Second Conference on Rheumatic Diseases held by the American Association for the Study and Control of Rheumatic Disease, June 2, 1933.

2 Parsons, Lawrence, and Harding, W. G., Jr. Fatal Cinchophen Poisoning. Report of Six Cases, *Ann. Int. Med.* **6** 514-517 (Oct.) 1932.

3 Parsons, Lawrence, and Harding, W. G., Jr. Cinchophen Administration. Jaundice as an Untoward Effect, *California & West. Med.* **37** 30-32 (July) 1932.

4 Grigg, W. K., and Jacobsen, V. C. Subacute Yellow Atrophy of the Liver Following Ingestion of Cinchophen and Allied Compounds, *Ann. Int. Med.* **6** 1280-1288 (April) 1933.

5 Still, G. F. On a Form of Chronic Joint Disease in Children, *Tr. Roy. Med.-Chir. Soc.* **80** 52, 1897. Dr. Reginald Fitz called my attention to this reference.

6 Sidel, Nathan, and Abrams, M. I. Jaundice in Arthritis. Its Analgesic Action, *New England J. Med.* **210** 181-182 (Jan. 25) 1934.

7 Borman, M. C. Jaundice in Arthritis, with Report of Two Cases, *Wisconsin M. J.* **35** 890-891 (Nov.) 1936.

MATERIAL FORMING THE BASIS OF THIS REPORT

The present report summarizes my further observations (table 1) on this phenomenon from studies made of thirty-one additional rheumatic patients who experienced similar dramatic remissions of symptoms coincident with various types of jaundice and, of equal importance, notes on four patients with chronic infectious (atrophic) arthritis and nine patients with miscellaneous articular or neuritic conditions (other

TABLE 1—*Effect of Jaundice on Thirty-One Patients with Rheumatic Disease*

Disease	Average Duration, Years	Jaundice			Remission				Subsequent Course				
		Type	No of Cases	Average Duration, Weeks	Duration, Weeks		Degree of Relief		As Before	Mild Recurrence	No Recurrence	Unknown	Died
					Average	Range	Complete	Almost Complete					
Chronic infectious arthritis	5.5	Intrahepatic (cinchophen)	8	4.5	13.5	5-43							
		Intrahepatic (other)	9	11.5	17.5	5-39	12	7	10	8	1		
		Obstructive (stone)	2	13.5	45.0	7-82	63%	57%					
Total			19	9.0*	18.5*								
Primary fibrositis	5.2	Intrahepatic (cinchophen)	6	4.8	18.0†	4-44†							
		Obstructive (stone)	2	3.0	54.0	5-104	9		3	4	1	1	
		Obstructive (cancer of ampulla of Vater)	1	14.0	44.0	‡	100%						
Total			9	5.6*									
Miscellaneous Lumbosacral and sciatic pain (2) hypertrophic arthritis of hips (Otto pelvis) (1)	2.3	Intrahepatic	3	5.0	5.0		1 33%	2 67%	2	1			

* General average

† If one patient's remission of three years is included the average is thirty nine weeks

‡ Until death occurred

than atrophic arthritis or primary fibrositis) who were *not* relieved by jaundice. Space does not permit inclusion of detailed protocols of all the cases in which sudden remission was noted. Details concerning one of these cases were presented elsewhere,⁸ data on representative cases are given herein.

Patients with Chronic Infectious (Atrophic) Arthritis Which Was Relieved by Jaundice—Representative Case. A housewife aged 55

8 Hench, P. S. A Clinic on Some Diseases of Joints. IV. The Inactivating Effect of Jaundice in Chronic Infectious (Atrophic) Arthritis and Fibrositis, *M. Clin. North America* 19: 573-583 (Sept.) 1935.

years had suffered for twelve years with severe chronic infectious polyarthritis which involved the shoulders, elbows, wrists, hands, hips and ankles. She had had much pain, stiffness and disability. Articular swelling usually was moderate but at times her "fingers were so swollen that they stuck right out," and she could hardly wear shoes because of the swelling. Walking was much restricted, and she needed help to do her housework.

In April 1933 she was bedridden for six weeks because of articular disability. In July she began to take "Cahill's pills" (containing cinchophen) and continued to take them intermittently for ten weeks. On September 16 she noted that she was jaundiced and that the urine was dark. Three days later (September 19) the articular pains began to fade, and on the fourth day of the jaundice (September 20) she noted "complete relief" from pain, stiffness, redness and swelling. She

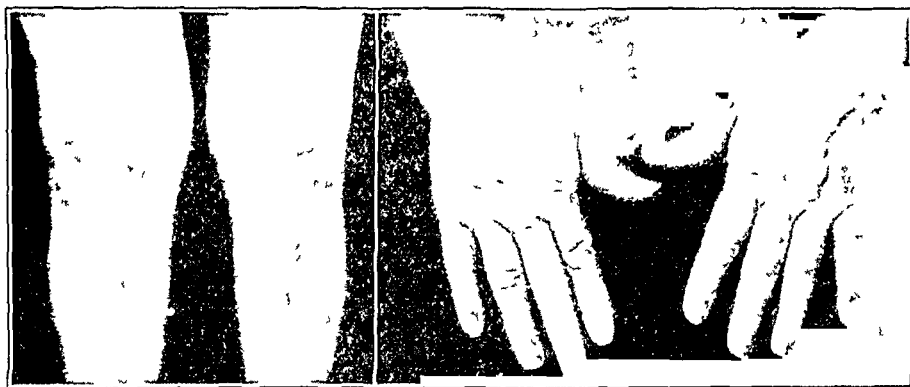


Fig. 1—The knees and hands of a woman aged 55 who had had chronic infectious (atrophic) arthritis for twelve years. She obtained complete symptomatic relief from pain, stiffness, redness and swelling during cinchophen jaundice. These photographs were taken three weeks after the disappearance of jaundice and two weeks after the return of the activity of the arthritis. One may note thickening of the phalangeal joints and swelling of the wrists and knees.

stated, "I was able to do all my housework and felt real well except for a poor appetite." A month later (October 20) the jaundice began to fade, but articular pains had not returned. On October 24 the patient first noted a return of slight pain and swelling in one hand. She then came to the Mayo Clinic.

On October 27 (at the clinic) she was icteric (grade 2+ on a scale with 4 indicating the most extreme condition). The concentration of serum bilirubin was 10.3 mg per hundred cubic centimeters, the van den Bergh reaction was direct. The knees and fingers were by then slightly swollen (fig. 1), but she said she "still had 90 per cent of the relief which jaundice brought to the joints." Ten days later, at the time

of her dismissal (November 6), the value for serum bilirubin had fallen to 4.8 mg (direct reaction), and the joints were becoming worse, although she still had "only one-third as much trouble as before the jaundice." In June 1934 (when she last wrote me) her knees were considerably affected, but other joints that had been painfully involved prior to the jaundice were still unaffected, nine months after the onset of the remission. She was moderately obese which may have been a factor in the early return of pain to the knees.

Synopsis of the Effect of Jaundice on Nineteen Patients with Chronic Infectious Arthritis. The effect of jaundice was noted by a total of nineteen patients who had chronic infectious arthritis, including the patient whose case has just been reported (table 1), the average duration of the disease was five and one-half years (range, one month to eighteen years). In eight of the nineteen cases of arthritis, intrahepatic jaundice due to cinchophen developed, the jaundice lasted for an average of four and one-half weeks (range, two to eight weeks). The remissions of symptoms lasted for an average of thirteen and one-half weeks (range, five to forty-three weeks).

In nine of the nineteen cases of arthritis, intrahepatic jaundice of different types developed. In six cases it was classified as catarrhal or epidemic infectious jaundice, and in the three other cases it was classified as due, respectively, to hepatitis and cholecystitis without stones, to hepatitis and portal cirrhosis with ascites and to syphilitic hepatitis (or possibly arsenphenamine jaundice). The average duration of the intrahepatic jaundice in these nine cases was eleven and one-half weeks (range, ten days to six months). The remissions induced thereby varied in length from five to thirty-nine weeks (average, seventeen and one-half weeks).

In the remaining two of these nineteen cases of arthritis, obstructive jaundice developed, being due to gallstones. The average duration of the jaundice was thirteen and one-half weeks and that of the remissions was forty-five weeks. The unusual average length of the jaundice and the remissions in these two cases resulted from the fact that one patient had a stone in the common bile duct which caused jaundice of varying intensity for about twenty-four weeks and a complete remission of symptoms for nineteen months (eighty-two weeks). In the other case jaundice of three weeks' duration produced a complete remission of articular symptoms for seven weeks.

Two of these nineteen arthritic patients experienced jaundice more than once, the result of each attack of jaundice has been included in these averages and will be discussed later.

In summary, the nineteen patients who had chronic infectious arthritis had jaundice which lasted on an average nine weeks and a

remission of articular symptoms which lasted on an average twice as long (eighteen and one-half weeks) Twelve (63 per cent) of the patients received complete relief from their active articular symptoms, and seven (37 per cent) of the patients had almost complete relief, for example, they had no pain while at rest and no swelling or tenderness but had slight aching after weight-bearing, or they had no stiffness or pain while at rest or on motion but had slight articular tenderness Relief from stiffness, of course, means relief from the articular or muscular stiffness due to active inflammation and spasm of muscles and joints and not that due to residual structural damage

Patients with Primary Fibrositis Which Was Relieved by Jaundice — Periarticular and extra-articular (as well as intra-articular) fibrous tissues are involved in practically all cases of chronic infectious arthritis, thus, associated or secondary fibrositis is a part of this disease In the following cases of primary fibrositis, however, there was no evidence of arthritis or of intra-articular disease Primary fibrositis is characterized by chronic stiffness, aching and soreness of muscles (intramuscular fibrositis) or of joints (periarticular fibrositis) or of both The condition presents no evidence of intra-articular disease, such as hydrops, significant swelling, roentgenographic alterations or deformity from intra-articular disintegration, nor does it give evidence of the systemic, clinical and chemical manifestations which make up the syndrome of chronic infectious arthritis, such as loss of weight, hypochromic anemia, increase in the sedimentation rate and increase in the nonfilamented cell count Periarticular fibrositis is often erroneously diagnosed as mild arthritis The criteria employed at the clinic for the diagnosis of primary fibrositis have been published⁹

Representative Case On Feb 15, 1935 a physician aged 64 suddenly acquired afebrile stiffness and soreness of the knees, elbows and shoulders, without redness or swelling The disability progressed, rapidly, so that by February 18 he had to use a cane in walking During the next week the degree of stiffness and soreness increased markedly, so that he was unable to walk, comb his hair, write or clothe himself He had great difficulty in feeding himself, and because of soreness, stiffness and weakness of the joints of the arms and hands he dropped a coffee cup on several occasions On March 5 he gave up his practice and went to a spa He was practically helpless, he could not feed or dress himself and required the services of a nurse night and day He was taken in a wheelchair for immersion baths and was lifted by attendants into the water Only a few hours of relief was afforded by

⁹ Slocumb, C H Differential Diagnosis of Periarticular Fibrositis and Arthritis, *J Lab & Clin Med* **22** 56-63 (Oct) 1936 Hench, P S Acute and Chronic Arthritis, in *Nelson Loose-Leaf Living Surgery*, New York, Thomas Nelson & Sons, 1935, vol 3, chap 1, pp 104-175

the baths, to augment this relief, cinchopyrine (cinchophen, aminopyrine calcium carbonate and colchicine) was given daily

Prior to March 10 the patient had severe pains and disability. On March 10 he thought his eyes were slightly yellow. On March 11 he noted frank jaundice, and on that day he said that his pains began to fade. This physician described the experience further as follows: "The next day (March 12) all articular symptoms were gone. I could walk freely to the bath. I thought the baths and medicine had cured me, so I dismissed both my nurses. By afternoon I felt so well that it seemed foolish to stay longer, so I walked downtown (a small town) for my railroad tickets, but that evening, on the advice of my physician, I decided to stay because of the jaundice and some nausea." During the next few days the patient walked freely about his hotel and to the baths and had no symptoms of rheumatism. On March 16 he went home, but because the jaundice persisted, he came to the Mayo Clinic on April 1.

The jaundice was then fading, the concentration of serum bilirubin was 3.4 mg (direct reaction). All the joints were entirely painless on voluntary and even on forced motion. There was no articular tenderness or aching or periarticular thickening. Jaundice lasted five weeks. The patient remained completely free from rheumatic disability for ten months. On Jan. 15, 1936, he first noted a return of mild pains in the joints, which have persisted (mildly) to the time of writing.

Synopsis of the Effect of Jaundice on Nine Patients with Fibrositis
Nine patients who had primary fibrositis, including the one whose case has just been reported, experienced complete symptomatic remissions coincident with jaundice (table 1). All had periarticular fibrositis, and three had intramuscular fibrositis also. The duration of the disease averaged five and one-fifth years. In six of these nine cases of fibrositis, intrahepatic jaundice was caused by cinchophen and lasted from three to ten weeks, with an average of four and four-fifths weeks. Excluding one case, the complete remissions of fibrositis lasted for an average of about eighteen weeks (range, four to forty-three weeks). One patient had no recurrence of symptoms for three years, when this patient is included, the average length of the remissions is raised from eighteen to thirty-nine weeks.

In three of the nine cases of fibrositis, obstructive jaundice developed, in two cases as a result of stones and in one case as a result of carcinoma of the ampulla of Vater. Jaundice from cholelithiasis lasted for an average of three weeks (range, one to five weeks), but the average length of the symptomatic remissions was fifty-four weeks, because one of these two patients, who had obstructive jaundice twice, had complete remission of fibrositis for two years after one of the attacks of cholelithiasis with jaundice. Otherwise the remissions lasted five weeks in the one case and five months after the second attack of

jaundice in the other case. In the case in which obstructive jaundice developed as a result of cancer of the ampulla of Vater, the jaundice lasted fourteen weeks prior to surgical relief of the biliary obstruction. The patient had had stiffness and soreness of many joints practically constantly for twenty years. At the clinic she stated that until the jaundice had begun she had not had any real relief of the articular symptoms in all the twenty years. Thereafter, until her death on July 19, 1934, the joints were free from symptoms, a remission of forty-four weeks.

In summary, in the nine cases of fibrositis, jaundice developed, with an average duration of five and three-fifths weeks. In every instance the symptomatic remission induced thereby was complete, and the patient was entirely free from symptoms of stiffness, soreness, tenderness or aching. This contrasts with the fact that only 63 per cent of the arthritic patients obtained complete relief, since the remaining 37 per cent had almost complete relief. One would expect a more complete effect in fibrositis, wherein pathologic changes are so much less pronounced than in chronic infectious arthritis.

Additional Patients Whose Articular Symptoms Were Relieved by Jaundice—With the onset of jaundice, two patients who had chronic lumbosacral and sciatic pains and one who had an Otto pelvis and hypertrophic arthritis of the hips were relieved of symptoms. The duration of their pains prior to jaundice averaged two and three-tenths years.

1. A man aged 44 years had severe pain in the lumbosacral and sciatic region after influenza in February 1934. He was in bed two weeks, and thereafter he could not work for three months. Less severe but annoying pains continued until March 1935, when the pain in the back became worse after he changed an automobile tire. He took 182 capsules of oxyiodide (cinchophen hydriodide) during the next few weeks and on April 1 noted slight jaundice, dark urine and light stools. He observed that on that day his back was definitely better. Either on April 3 or 7 he said to a relative, "My backache is gone completely. It seems strange to me that my back has stopped hurting since my jaundice came out. I wonder if there is any connection between the two."

The patient was seen at the clinic about three weeks later (May 29), still deeply jaundiced (serum bilirubin content, 21.4 mg, direct reaction). He stated that prior to the development of jaundice, he had had considerable difficulty sliding on and off a high bank clerk's stool and changing his position in bed. At the clinic he had full, free motion of the spinal column and extremities and no pain. I could not elicit any tenderness or pain even by pounding with my fist over the previously affected regions or by subjecting his joints to strenuous passive motion. Roentgenograms gave evidence of slight narrowing of the lumbosacral joint and hypertrophic changes of the right lumbosacral facet and of the right fourth and fifth lumbar facets. It was reported that neurotropic streptococci were recoverable from the nasopharynx and that there was no evidence of an increase in antistreptococcal immune bodies in the presence of jaundice, the significance thereof will be discussed later.

The value for serum bilirubin rose to 28.6 mg and then fell to 6 mg at the time of the patient's dismissal, May 23. A month later the jaundice (of eleven

weeks' duration) had ended. The analgesia lasted at least that long. The patient did not recall just when his pains began to recur, but for the two years prior to May 1937 his back had been "much less painful than it used to be before the jaundice."

2 Another patient whose lumbosacral and sciatic pain was relieved by jaundice was a man aged 49 who had fever and severe pain in the small of the back, right hip and thigh late in April 1934. The condition had been diagnosed as due to influenza and sciatica. In June, after being in bed for six weeks with severe pain, he began to use crutches, and in the middle of July he took six bottles of a patent remedy for rheumatism because of chronic backache. On October 8 he became jaundiced. The next day he had fever and epigastric distress, but, he said, "On waking I noticed I had no rheumatism, and my back felt fine." For about a week he had no pain, then slight pain ("20 per cent as much as before") returned. Jaundice lasted a short time, starting to fade about October 11, when he came to the clinic.

The value for serum bilirubin was 4.4 mg (direct reaction). The spinal column was stiff, and there was some tenderness in the right iliac and gluteal regions. His pains, however, were much less severe than formerly. On October 19, when the value for serum bilirubin had fallen to 1.6 mg (direct reaction), his backache became as severe as before the occurrence of jaundice. The diagnosis was spondylitis, cirrhosis of the liver, with jaundice, and splenomegaly. There was some discussion as to how much (if any) of the symptomatology might be due to undulant fever. The serum agglutinated *Brucella abortus* in a dilution of 1 to 160; he had lost sixteen calves because of disease due to that organism in March.

Moderate jaundice of short duration apparently had relieved the patient's backache and sciatic pain completely for a few days and partially for a few days more. In January 1935 he had no pain except in the neck.

3 A man aged 49 had had pain in the left hip and thigh for six years. Jaundice, presumably of the spontaneous catarrhal type, appeared, his local physician noted an icterus index of 20 (roughly analogous to a value for serum bilirubin of about 3 mg). Jaundice lasted about three weeks, part of this time he was completely relieved, the rest of the three weeks he was notably, but incompletely, relieved of pain. At the clinic, roentgenograms revealed marked hypertrophic arthritis of both hips, with protrusion of the femoral head into the acetabulum. The condition was thought to be not ordinary chronic infectious (atrophic) arthritis or simple senescent (hypertrophic) arthritis but hypertrophic arthritis associated with an Otto pelvis. The patient came to the clinic on May 23, 1934, a week after the jaundice had left, pain was then returning in the usual situations. The value for serum bilirubin was only 1.4 mg (direct reaction).

The conditions presented by these three patients were admittedly not as clearcut and the effects of coincident jaundice were not as dramatic as those of the patients with arthritis and fibrositis, but the reports are included in order that it may be considered to what degree the analgesic or inactivating effect of jaundice may or may not be relatively specific for diseases more obviously rheumatic.

Patients with Arthritis or Fibrositis Who Had Repeated Jaundice—Two of the patients who had arthritis and two of those who had fibrositis had jaundice more than once (table 2).

A woman aged 49, who had had chronic infectious arthritis (fig 2) uninterruptedly for fifteen years had marked spontaneous painless jaundice which lasted twenty-five weeks. A complete symptomatic remission developed and lasted nine months, then the symptoms returned as before. Four years later, "slight" jaundice developed after she had taken only 4 tablets of cinchophen. The jaundice lasted three weeks, and the patient had no relief from the arthritis therewith. The following year, without further medication, "very mild" (spontaneous) jaundice developed, lasted two weeks and produced no symptomatic remission.

This indicates, again, as noted in my first report, that mild jaundice will not produce the phenomenon, a certain intensity of jaundice is necessary to invoke it.

TABLE 2—*Effect of Repeated Jaundice on Four Patients with Arthritis or Fibrositis* *

Diagnosis	Duration, of Disease Years	Jaundice			Remissions		Subsequent Course
		Type	Degree	Length, Weeks	Degree	Length, Months	
Chronic infectious arthritis	15	1 Spontaneous painless	Marked	25	Complete	9	As before
	19	2 Cinchophen ? (4 pills)	Slight	3	None		
	20	3 "Spontaneous"	Very mild	2	None		
Periarticular fibrositis	1/12	1 Obstructive (stone)	Moderate	1	Complete	24	Pains returned
	2½	2 Obstructive	Marked	3	Complete	5+	No pain to date
Diffuse fibrositis and chronic hypertrophic arthritis (traumatic and senescent)	14	1 Cinchophen ?	?	4 5	Complete	8	As before
	15	2 Cinchophen	Serum bilirubin value of 12.7 mg	6	Complete	4¼	As before
Chronic infectious arthritis	9	1 Cholecystitis, hepatitis	?	6	Partial	?	
	11	2 Cholecystitis hepatitis	Moderate	1	Complete	¾	As before

* Symptomatic remissions were produced when marked or moderate jaundice was present, mild jaundice had no effect on the rheumatic symptoms.

Three other patients, however, received marked or complete amelioration of articular symptoms on two occasions each (table 2). In each instance the jaundice was moderately severe or marked. Insufficient data are at hand to make it possible to state whether subsequent periods of jaundice are more or less effective in producing prolonged analgesia than is an initial attack of jaundice.

Patients Whose Articular Disease Was Not Affected by Jaundice—At the time of my first report ¹ I had not seen a patient with jaundice who had not received more or less complete, although temporary, relief from preexisting rheumatic pain. However, records of the clinic contained data on three patients, two with chronic infectious arthritis, one

with sacro-iliac pain and one with sciatic pain, which indicated that jaundice was not always associated with relief from pain, these cases were discussed in the first report as cases 13 to 15

Observations have been made on thirteen additional patients who were unrelieved by jaundice (table 3) In the presence of mild jaundice, four patients with chronic infectious arthritis were unrelieved of arthritic symptoms Three patients who had gout suffered from two or more painful attacks of gouty arthritis in the presence of jaundice which, although mild in two cases, was fairly intense in one case In one patient jaundice of uncertain intensity developed during the "silent or prodromal phase" of rheumatic fever, the jaundice did not cause the subsequent attack of rheumatic polyarthritis to be aborted In the presence of fairly intense jaundice, there was marked articular pain in

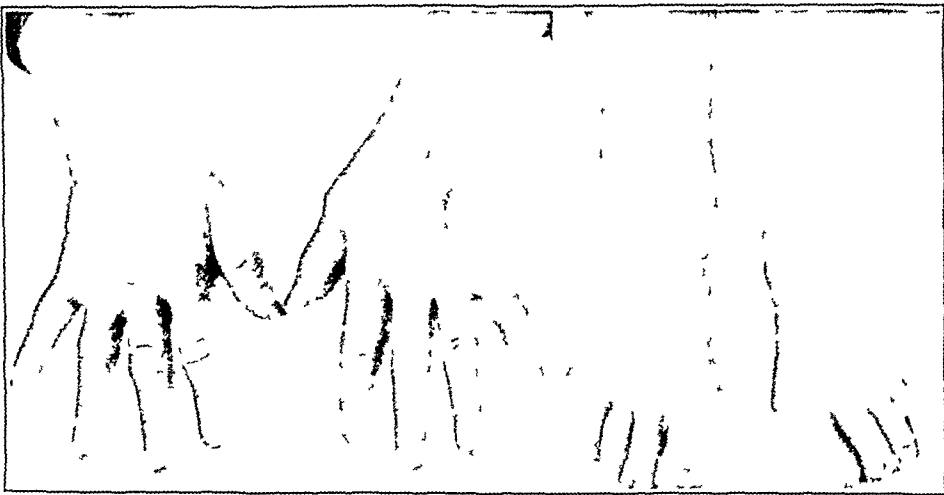


Fig 2—The feet and hands of a woman aged 49 who had had chronic infectious arthritis for fifteen years She obtained complete symptomatic relief which lasted for nine months, it began with the onset of a spontaneous painless but marked jaundice of twenty-five weeks' duration Two subsequent short attacks of mild jaundice produced no relief of the articular symptoms These photographs were taken after the end of the symptomatic relief One may note swelling of the right wrist, of certain midphalangeal joints and of the ankles

a case of a juxta-articular malignant growth and in two cases of "toxic or infectious arthralgia," and marked neuritic pain was present in a case of postherpetic neuralgia and in a case of ischemic neuritis

In some of these cases, particularly those of chronic infectious arthritis, the symptoms may not have been ameliorated because the jaundice was slight, below the "zone of therapeutic effectiveness" In other cases, however, the jaundice was of an intensity which is effective in chronic infectious arthritis, yet articular symptoms were not relieved These observations suggest, therefore, (1) that the phenomenon is quantitative, dependent on a certain intensity of jaundice, and (2) that

it may be relatively specific for infectious (atrophic) arthritis and for primary fibrositis. Further studies of cases in which relief is *not* produced by jaundice may yield data on the mechanism and specificity of the reaction in the cases in which relief is obtained.

TABLE 3—*Observations on Thirteen Patients Whose Articular or Neuritic Symptoms Were Not Relieved by Jaundice*

Painful Condition Apparently Unrelieved by Jaundice	Jaundice		Intensity
	Type	Duration	
1 Chronic infectious arthritis, 4 yr	Obstructive jaundice	3 wk	Mild, "eyes a bit yellow"
2 Chronic infectious arthritis, 2 yr	Cinchophen	8 wk (?)	Uncertain, mild (?), never in bed no relief during 2 pregnancies
3 Chronic infectious arthritis, 9 yr	Jaundice with agranulocytosis (aminopyrine?)	4 days	Mild, maximum serum bilirubin value, 3.2 mg, direct van den Bergh reaction
4 Chronic infectious arthritis (?), 8 yr creaky painful joints, neuromuscular pains	Hemolytic		Serum bilirubin value, 3.8 mg indirect van den Bergh reaction
5 Gouty arthritis, 2 attacks	Obstructive jaundice and cancer of pancreas	2 mo	Serum bilirubin value, 14.5 mg during one short painful attack
6 Gouty arthritis, several attacks	Hemolytic		Uncertain, acute gout after splenectomy when serum bilirubin value was 1.3 mg, direct van den Bergh reaction
7 Gouty arthritis, several attacks	Hemolytic		Fluctuating, serum bilirubin value, 6.3 mg direct van den Bergh reaction during 1 attack
8 Acute rheumatic fever, third attack	Catarrhal jaundice 4 days later, onset of rheumatic fever	1 wk	Uncertain
9 Sternoclavicular swelling, acutely painful metastasis (?) specific infection?	Obstructive jaundice cancer of pancreas		Serum bilirubin value, 11.9 mg falling
10 Arthralgia, recurrent, febrile	Jaundice from hepatitis cirrhosis	6 yr	Uncertain, at one time serum bilirubin value, 7 mg, direct van den Bergh reaction
11 Arthralgia painful tender joints hydrops in one	"Infectious"	Several mo	Serum bilirubin value falling 6.4 to 2 mg direct van den Bergh reaction
12 Neuralgia, post herpetic	Obstructive, recurrent (cholecystitis stone in common duct), 3 or 4 attacks of jaundice since onset of neuralgia		Uncertain "pretty yellow each time"
13 Neuritis (ischemic) after gynergen	Partial stricture of common duct		Serum bilirubin value 11 mg falling

* Four patients had chronic infectious (atrophic) arthritis and nine had articular or neuritic symptoms from conditions other than chronic infectious arthritis or fibrositis. The observations suggest that the phenomenon is relatively specific for chronic infectious arthritis and for primary fibrositis but, even so, it bears a quantitative relation to the intensity of the jaundice.

In connection with the beneficial effect which jaundice seems to have on certain rheumatic diseases and in view of cases 10 and 11 (table 3) particularly the former, wherein arthralgia seemed to be a symptom coincident with febrile attacks of deepening jaundice it is of interest

to note that Freund¹⁰ has briefly described "arthritis posticterica," Glénard and Françon¹¹ have discussed *rheumatismes chronique d'origine hépato-biliaire*, and recent French monographs¹² on diseases of joints include paragraphs on *le rhumatisme chronique biliaire* (enlargement of the ends of the bones, synovitis and pains in the joints—a form of osteoarthriopathy rather than a type of arthritis), described by Gilbert and Fournier (1895),¹³ by Gilbert and Lereboullet (1902)¹⁴ and by Wynn (1904)¹⁵ This entity has not been described in the United States, so far as I am aware, and I am not sufficiently familiar with it to know whether it should be regarded as established Taylor¹⁶ (1895) described the case of a young man who had "multilobular and unilobular hepatic cirrhosis" from the age of 6 years and who died of pyemia at the age of 20 During the last week of his life and while he was jaundiced (degree unstated), acute polyarthritis developed His condition probably was pyemic arthritis, however, it was not "biliary rheumatism" Rolleston and McNee¹⁷ (1929) stated that toxic and pyemic arthritis may occur in cases of single or "tropical liver abscess," such as that caused by *Endamoeba histolytica* They said they regarded biliary rheumatism skeptically In his recent monograph Weiss¹⁸ (1935), however, mentioned stiffness of the articulations, especially of the hands and of the nape of the neck, as one of the minor diagnostic signs of latent hepatic insufficiency In whatever manner my own two cases should be labeled, obviously the arthralgia and the soreness of fibrous tissue were not due to primary fibrositis or to ordinary chronic infectious arthritis

10 Freund, Ernst Gelenkerkrankungen Einführung in die Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1929, p 139

11 Weissenbach, R J, Glénard, R, and Françon, F Rheumatismes chronique d'origine hépato-biliaire, Nutrition 2 117-138, 1932

12 Marinesco, G Rheumatisme chronique par auto-intoxication, in Roger, G E H, Widal, F, and Teissier, P J Nouveau traité de médecine et de thérapeutique, Paris, Masson & Cie, 1924, pp 552-553 Mouriquand, Georges, and Michel, Paul Rheumatisme chronique, in Weill, A Maladies de la nutrition, Paris, A Malome et fils, 1922, vol 23, p 612

13 Gilbert, A, and Fournier, L La cirrhose hypertrophique avec ictère chez les enfants, Compt rend Soc de biol 47 419-420, 1895

14 Gilbert, A, and Lereboullet, P Le doigt hippocratique dans les cirrhoses biliaires, Gaz hebdomadaire de médecine 7 1-4, 1902

15 Wynn, W H Secondary Hypertrophic Osteo-Arthriopathy, Birmingham M Rev 55 139-155, 212-228 and 282-302, 1904

16 Taylor, Frederick Cases of Cirrhosis of the Liver in Children, with Some Remarks on Cirrhosis [case 2], Guy's Hosp Rep 52 53, 1895

17 Rolleston, Humphrey, and McNee, J W Diseases of the Liver, Gallbladder and Bile Ducts, ed 3, London, The Macmillan Company, 1929

18 Weiss, Samuel Diseases of the Liver, Gallbladder, Ducts and Pancreas Their Diagnosis and Treatment, New York, Paul B Hoeber, Inc, 1935, p 282

CHARACTERISTICS OF THE PHENOMENON, RECAPITULATION

Specificity—On the basis of present information, then, the phenomenon seems relatively specific for chronic infectious arthritis and for primary fibrositis (including certain cases of sciatica). I have not had the opportunity to see the phenomenon in a case in which disability prior to jaundice was chiefly or solely due to senescent hypertrophic arthritis. However, four of the patients who received complete relief from articular and muscular symptoms when jaundice appeared had this form of arthritis coincidentally with the main disease—chronic infectious arthritis in two cases and chronic periarticular and intramuscular fibrositis in two cases. When each of the patients came to the clinic in the course of, or after, the attack of jaundice, roentgenographic or objective evidences of symptomless senescent arthritis were visible (spurs in the lumbar or cervical portions of the spinal column and Heberden's nodes), but the history indicated that the previous disability, which had been temporarily inactivated completely by jaundice, was mainly if not wholly due to rheumatism of another type—infectious arthritis or diffuse primary fibrositis. It could not be determined whether the patient had had symptomatic, if incidental, senescent arthritis which also had been made asymptomatic, or whether the senescent arthritis had been asymptomatic before the development of jaundice.

Aside from the one inconclusive observation on rheumatic fever, I have not seen a patient who had this disease and coincident jaundice. As has been noted, gouty arthritis apparently may be acute and painful, in spite of fairly severe jaundice. At least two patients who had arthralgia of undetermined type, one patient with neuralgia and one with neuritis experienced pain in the presence of jaundice, not of marked intensity, however. Further observations may indicate that more intense degrees of jaundice than those thus far encountered in association with these diseases may be more effective, stressing the quantitative rather than the specific nature of the reaction.

Relative Effectiveness of Different Types of Jaundice—The phenomenon apparently can be precipitated by almost any type of obstructive or hepatogenous jaundice provided it is intense enough. Most of the common types of jaundice are represented in the group of conditions in which relief was obtained. The effectiveness of these types of jaundice seems to be more quantitative than qualitative. The data in table 1 seem to suggest that obstructive jaundice due to stones produced longer remissions than intrahepatic jaundice. But this conclusion, based on a study of only four cases of obstructive jaundice, in two of which the jaundice was inordinately prolonged, should not be accepted as final. No instance of "successful" hemolytic jaundice is included, probably because in none of the three cases in which hemolytic jaundice occurred was the con-

centration of serum bilirubin particularly high, indeed it rarely ever is high in this type of jaundice. It remains to be noted whether the phenomenon may occur in the presence of severe hemolytic jaundice. To aid the search for the responsible agent in jaundice it is important to determine this point because of the chemical differences between hemolytic and other types of icterus.

Promptness of the Reaction—Data on the time of appearance of the analgesia as it occurred in this second series of patients agree with those noted in my first series. The thirty-one patients of this series had thirty-four effective periods of jaundice, three having had more than one such period. In sixteen instances the patients were not sure of the exact time relation between the onset of recognized visible jaundice and the onset of relief of pain and were content with the statement that when the jaundice appeared (or with the onset of jaundice), the pain disappeared. In general, the onset of relief was noted promptly with the appearance of visible jaundice. Relief of pain was first noted on the first day of visible jaundice three times, on the second day four times and on the third day three times. Three patients who were disturbed by intestinal symptoms coincident with jaundice stated that toward the end of the first week they suddenly realized that the rheumatism was gone. It is likely that analgesia may have occurred sooner and may have been unrecognized owing to concern over the jaundice.

One of the patients in my first series (case 16) was rather insistent that the swelling and pain in the joints disappeared about six weeks before the onset of visible jaundice but with the onset of the early pre-icteric symptoms of toxic (cinchophen) hepatitis. So, too, four patients of this series stated that, according to their recollection, definite analgesia appeared several days before jaundice was noted. One patient noted it "when the urine began to be dark, one week before the jaundice was noticeable." Another, whose case will be described briefly hereafter, noted analgesia "one or two days before jaundice." One patient who experienced the phenomenon twice, dated the first period of analgesia as beginning one week before and the second period three to six days before the onset of jaundice. The fourth patient I examined in May 1934 because of severe spondylitis, which was still active after eighteen years. He was unable to work and could walk only three blocks with a cane. He returned to the clinic on December 17 with severe hepatitis, jaundice and ascites. His jaundice was first noted about September 1, but, he stated, "During the first week of August I began to get well awfully fast, and within two weeks my rheumatism was cured. My joints feel so well I think it will never return." He could walk at least three fourths of a mile (a kilometer) without a cane, and he said he felt better than he had for twenty years. The concentration of serum

bilirubin was 15.4 mg (direct reaction) Roentgenograms revealed marked spondylitis of the infectious (atrophic, rhizomelic or ankylosing) type. Examination revealed no soreness or tenderness anywhere, merely residual, inactive, or symptomless, spondylitis. The patient was dismissed on December 28 and died on March 12, 1935 having had, according to his local physician, "very little active arthritis after the jaundice."

Too much credence cannot be given these statements suggesting an analgesic effect from subclinical jaundice, because patients differ greatly as to the keenness of their observations. A slight or even a definite visible jaundice might well have escaped notice for the first few days. In cases in which relief presumably was noted some time before jaundice was visible, it must be considered whether such remissions materially preceding jaundice were coincidental and unrelated to the subsequent jaundice or whether potent subclinical icterus was present. Further observations must determine whether the phenomenon can occur in the preicteric phase of jaundice, with low concentrations of serum bilirubin.

Completeness of Relief Provided by the Phenomenon—Conservatism prompted the description of the reaction in the first report as "the analgesic effect of jaundice." Although relief of pain is the dominant effect, I believe that there is more to the phenomenon than analgesia. Stiffness and muscular spasm were notably relieved, soreness and tenderness were reduced and frequently even swelling was diminished materially. It must not be supposed, however, that residual periarticular thickening or stiffness, due to ankylosis or other structural damage, was reduced. The only symptoms affected were active inflammation in joints and only that amount of stiffness of joints which was due to active inflammation in and stiffness and spasm of surrounding muscles. Because these symptoms, as well as pain, were so frequently relieved, the analgesia must be regarded not as simple, merely a deadening of pained nerves, but of greater significance, an analgesia resulting from improvement in the underlying chemiopathologic state. Hence, "the inactivating effect of jaundice" was the term used later.⁸

Of the thirty-one patients, twenty-two (all those with fibrositis and 63 per cent of those with arthritis) obtained complete relief from pain and considered the disease symptomless. In seven cases of infectious arthritis, in one of lumbosacral and sciatic pain and in one of hypertrophic arthritis of the hips, relief was marked but incomplete.

Obviousness of the Phenomenon—After my first report, criticism was offered that perhaps the patients had been permitted to answer leading questions in the manner desired by the questioner. In this regard I may say that the earlier cases were discovered chiefly if not solely by me but many of the patients of this second series first volunteered the

characteristic and revealing remarks to my associates in other departments of the clinic, some of whom were unfamiliar with this study. Most impressive were the remarks which patients made to persons who were not familiar with the phenomenon—relatives, friends or the local physician, who was unaware of it. These informative remarks were either voluntarily recounted or, at most, were the otherwise unguided answers to the question "When you first noticed the effect you have mentioned, did you discuss it with those about you?"

The following selection of remarks provides evidence of the obviousness (and verity) of the phenomenon and of the perception of it by the patients.

1 A woman said "When the jaundice came, to my surprise I found that I could do things with my joints that I hadn't been able to do for many months. It was a revelation to me, and when friends asked about my rheumatism I told them it had suddenly left me—for which I was very thankful." Concerning this patient her physician wrote me "Her arthritis disappeared through the back door as the jaundice came in the front door."⁸

2 A man said "My rheumatism disappeared, although before the jaundice my neck was as stiff as if set in cement (from muscle stiffness).

3 A woman said "Before the jaundice developed I had to let some of my housework slide. After the jaundice came, I did it all. I felt so well I didn't go to my doctor until two weeks after the jaundice came on."

4 A man said "I would trade my rheumatism for jaundice any time if I could feel sure it wouldn't come back."

5 A woman said "My wrists and fingers were badly swollen. I couldn't raise my arms or comb my hair. But within fourteen hours of the time the jaundice appeared [it lasted only three or four days], I could move all over. The swelling and stiffness left my hands. My joints didn't hurt for three weeks. Then the pains began to come back."

6 A man said to a relative "What has become of my rheumatism?" To his local physician he said "Since the beginning of this trouble [jaundice] I've hardly noticed I have rheumatism. I've had joint pains every day for two years, and I've never been so free from them as I am now."

7 A man said "I told my brother-in-law that the only time I've really felt decent since the beginning of my rheumatism was when I had the yellow jaundice. I was very limber right after the jaundice. It was harvest time, and I worked the machinery easily."

8 A man said "Since the jaundice came, the rheumatism has been cured. At least the jaundice has done that for me. The way to cure rheumatism is to give a fellow jaundice and then cure the jaundice!"

In spite of the general unreliability of testimonials and voluntary contributions of laymen, the following letter seems worthy of inclusion, as it affords further evidence of the obviousness and nature of the phenomenon as it occurred in the case of a hopelessly crippled patient (not listed in this series). The patient had come to the clinic in 1926, at the age of 16 years, with curvature and limitation of motion of the

entire spinal column due to marked spondylitis. Thereafter he had become progressively disabled, in spite of various treatments. In 1935, inspired by newspaper accounts of the beneficial effect of malarial fever on syphilis and of artificial fever on gonorrhea, he wrote to Dr. Melvin Henderson as follows:

I have noticed in newspapers that one sickness may relieve another. I wish to report an experience I had in 1932. At that time I was almost completely disabled. I could only be stood on my feet to take sometimes none, sometimes as many as ten steps. Although I had taken no medicine except Kruschen salts occasionally, indigestion suddenly developed, without pain, perhaps from overeating. Four days later I noticed that my legs were less sore and more limber. On the fifth day my eyes were yellow and my urine was dark. I could stand on my feet, and my legs felt good. As the jaundice continued I could walk a few feet farther every day. The inflammation subsided in my worst joints. Most of the pain disappeared. In joints that were moderately affected, the stiffness was relieved. Although some of my joints were still completely stiffened, I was then able to shuffle 50 to 75 feet. The jaundice [apparently of moderate intensity] lasted one or two months. My joints were relieved for four to six months, then they slowly stiffened up again.

The letter concluded:

Now [1935] I can be stood up but can't walk a step. My outlook is hopeless, and I want to offer myself for experimentation. Since the discomfort of my indigestion was mild compared with the sore joints, I have often wished I could turn yellow as a pumpkin. I have frequently deliberately overeaten but have never found the right combination again. *In the explanation of this incident may lie the key to relief or cure of this disease.*

The statement is his, the italics are mine.

Although the majority of the patients recognized a connection between their remissions and the jaundice, as their remarks indicate, some noted the relief of symptoms but ascribed it to factors other than jaundice. Thus, the physician whose fibrositis was dramatically relieved, as previously noted herein (the representative case under the heading "Patients with Primary Fibrositis Which Was Relieved by Jaundice"), ascribed his relief to the baths which had given him practically no relief up to the first day of the appearance of jaundice. So, too, an arthritic woman with an abiding faith in the virtues of narcotics had cholecystic colic at 10 o'clock one morning. A hypodermic injection of morphine was given at 5 p. m. The next day she was jaundiced, and by night her arthritic pains (of five years' duration) had entirely left the shoulder and hands and had almost entirely left the knees. Later, the articular symptoms were completely relieved and remained so for three weeks, an effect she ascribed entirely to the single injection of morphine.

Relation Between the Degree of Symptomatic Relief and the Intensity and Duration of Jaundice—The intensity and the duration of jaundice

are by no means always interdependent, but, in general, intense jaundice lasts longer than mild jaundice, hence the two factors are related and in these cases were definitely so. Thus, they can be considered together. All the patients with fibrositis received complete relief (for variable periods), although the jaundice of some was moderate and that of others was marked. Among the arthritic patients who were markedly but incompletely relieved of pain were some whose jaundice seemed to be as deep and as long continued as that of those whose pain was completely relieved. Several factors prevent establishment of definite correlation for this group of patients. There were too many variables—the duration, activity and extension of the arthritis, and the type, duration and intensity of the jaundice. Furthermore, some of the patients were not seen at the clinic until some time after the jaundice had cleared, and the intensity of the condition was not established definitely. Some patients came to the clinic while the jaundice was receding, and the previous maximal intensity of the jaundice could not be estimated. In spite of these difficulties, it seemed evident that the generalization made in the first report was essentially correct. The reaction was apparently quantitative. The concentration of serum bilirubin did not exactly parallel the completeness of the remission, but it seemed to have a relation thereto. "The zone of therapeutic effectiveness" seemed to begin generally at a level of about 8 to 10 mg. of bilirubin and to continue at levels above that concentration. This generalization will need to be modified if it can be shown that relief really does begin occasionally in the stage of subclinical jaundice.

Relation Between the Length of the Remission and the Intensity and Duration of the Jaundice—The same factors that prevented deductions on the previous point interfered with conclusions on this point. In general, the longer and more intense the jaundice, the longer the remission. However, there was much variability. Thus, moderate jaundice of three weeks' duration was followed by a remission of only five weeks in one case and of three to four months in another. In still another case moderate jaundice of only ten days' duration was associated with marked (grade 3, not grade 4) relief for three or four months.

End Result of the Phenomenon—With few exceptions, the effect of jaundice has proved to be temporary, not permanent. A lasting cure is not provided or to be expected. Nevertheless, the phenomenon has given such welcome relief of articular symptoms, such an impressive "vacation from rheumatism," that many have expressed themselves as being satisfied with the trade of rheumatism for jaundice and have wished the trade could be permanent. To fifteen (48 per cent) of the thirty-one patients, rheumatic symptoms and disability returned as before. To thirteen patients (42 per cent) the rheumatic symptoms returned but

in distinctly milder form. The subsequent courses in the remaining three cases were as follows. One patient died of cancer, one patient has not been heard from and one patient with fibrositis has had a remission which still continues after three years and nine months.

The symptoms of one patient who had severe arthritis returned only after ten months of complete relief, and those of another, after nineteen months of complete relief. Another arthritic patient had complete relief for a while, after which marked, although incomplete, relief persisted for two years, several of his previously affected joints are still asymptomatic, and only his shoulders hurt when he lies on them. Return of symptoms of fibrositis generally was delayed longer. Periods of jaundice for three to ten weeks induced the following complete remissions in cases of fibrositis for four and a half, five, six, eight and ten (in two cases) months, two years, three years and three years and nine months, respectively.

SPECULATIONS CONCERNING THE AGENT RESPONSIBLE FOR THE PHENOMENON

The agent responsible for the phenomenon and the mechanism whereby it acts have not been determined. Several possible agents have been considered. The responsible agent, substance x, may be a normal or an abnormal constituent of bile, or it may be a product of hepatic damage.

Bilirubin—Obviously, in jaundice, bilirubin seems to be the most likely agent responsible for the effect. It might be argued that the tissues of arthritic patients lack sufficient bilirubin and that jaundice supplies the deficiency. This idea is particularly attractive in view of Race's¹⁹ recent finding that the icterus index and the concentration of serum bilirubin are likely to be somewhat low among patients who have rheumatoid arthritis. Though the concentration of serum bilirubin of his patients who had rheumatic diseases was somewhat lower than that of the controls, the deficiency of bilirubin was small and was not the chief cause of the low icterus index.

There are several reasons why a hypothesis of deficiency of bilirubin of tissues has been unsatisfactory. First, remissions of the symptoms of arthritis may be induced by states other than jaundice, notably pregnancy, in which hyperbilirubinemia does not occur. Nature probably does not cure arthritis even temporarily in two totally different ways, in the last analysis, the agent responsible for the relief of arthritic

¹⁹ Race, Joseph. Biochemical Investigations in Chronic Rheumatic Diseases in Reports on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1935, no. 1, pp. 55-71, Vitamins and Rheumatic Diseases, in Reports on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1937, no. 3, pp. 30-48.

symptoms probably is the same in the presence both of pregnancy and of jaundice, although the mechanism for developing the agent is different. Second, in respect to the jaundiced arthritic patients, the relation between the depth of the jaundice (the concentration of serum bilirubin) and the phenomenon of symptomatic relief, although close was not absolute. In many cases the analgesia lasted long after the serum bilirubin (and presumably the tissue bilirubin) content had returned to normal. Furthermore, if the statements of the patients who noted relief before the onset of visible jaundice are reliable, they indicate that hyperbilirubinemia was not necessary or that only slight hyperbilirubinemia was necessary to produce the phenomenon. Since other observations on the ineffectiveness of slight, even if definitely visible, jaundice (5 to 8 mg. of serum bilirubin) have made the latter deduction untenable, no final conclusion as to the role of bilirubin can now be made. The phenomenon occurs consistently in the presence of fairly intense hyperbilirubinemia but is generally absent when hyperbilirubinemia is not present or is only slight. This seems to incriminate bilirubin, but if the mechanism of relief in pregnancy is ultimately the same as in jaundice, one must conclude that an amount of bilirubin that will produce icterus is not necessary for the phenomenon. Perhaps in the presence of pregnancy and of jaundice, a special potent form of bilirubin, a derivative of bilirubin (and not "ordinary bilirubin") or perhaps an allied compound, is the responsible agent and is effective even in amounts that do not cause pigmentation.

Bile Salts—These may be the responsible agents. In certain types of hepatic disease accompanied with jaundice, the content of bile salts presumably is increased in the blood, but in other types of hepatic disease accompanied with jaundice it is apparently decreased. Until adequate methods for determination of bile salts in the blood are available, opinion on the possible connection between bile salts and the phenomenon under discussion must be held in abeyance.

Hepatic Autolysate—A product of hepatic injury, some hepatic autolysate, may be the responsible agent. Snell²⁰ has said that he inclines to this view. I hope the responsible agent is something simpler to identify than a hepatic autolysate. It seems more likely to me that the responsible agent is some product which is normal, not abnormal, to the tissues helped thereby.

Special Diet—One of Pemberton's²¹ patients (his case 53) apparently experienced the phenomenon in the course of jaundice, but the

20 Snell, A. M., cited by Hench.⁸

21 Pemberton, Ralph. Studies on Arthritis in the Army, Based on Four Hundred Cases. V. Roentgen-Ray Evidences, Clinical Considerations, Treatment Summary, Conclusions and Clinical Abstracts of Cases Studied [Case 53], *Arch Int Med* 25:398 (April) 1920.

relief was ascribed to the dietary restrictions incident to jaundice. The phenomenon cannot be attributable to the coincidental use of a diet low in calories or in carbohydrate. Many of the patients while in the hospital under the care of Drs. Snell, Wen, Comfort, Wilbur and myself were given 400 to 500 Gm of carbohydrate daily (bread, cereals, potatoes, crackers, jellies, cakes, fruit juices and candy between meals). They were on this so-called supportive diet for hepatic disease for three to five weeks in the hospital and for at least three to six months thereafter. While in the hospital they were generally given also an average of 100 Gm of sugar intravenously daily for three weeks. Glycosuria often was produced, but the analgesia and reduction of stiffness and swelling of joints were in no way disturbed by this large intake of carbohydrate daily for many weeks.

SPECULATION CONCERNING CIRCUMSTANCES THAT MIGHT BE RESPONSIBLE FOR THE PHENOMENON

It has been suggested that the responsible factor is not a chemical substance but a set of circumstances incident to jaundice—simple sedation, rest and reduction of trauma, dehydration and counterirritation.

Simple Sedation—It has been argued that perhaps one of the chemical compounds concerned in some way with jaundice is a sedative substance, nonspecific for rheumatism, which dulls the sensorium and diminishes perception of pain by the markedly jaundiced patient. This explanation is not satisfactory, because the phenomenon often includes reduction of stiffness and swelling as well as analgesia. Furthermore, the majority of these jaundiced arthritic patients are physically and mentally active and alert, in spite of the jaundice, as photographs and my motion pictures of them indicate. If jaundice provides simple nonspecific analgesia, it would probably have been noted previously in association with many diseases. As far as I am aware, it has not been noted that visceral pains with jaundice are, in general, any less severe than those without jaundice. Were simple general analgesia provided, one of the gouty patients (case 5, table 3), the patient with the painful sterno-clavicular swelling (case 9) and the one with the ischemic neuritis (case 13) should have obtained some relief or more relief than they did, because the jaundice they had was fairly intense and the level of the serum bilirubin was in the "zone of therapeutic effectiveness."

Rest, Reduction of Trauma—It has been suggested that rest in bed or a sharp reduction of activity and of trauma to joints in the course of jaundice was responsible for the relief of pain. Rest cannot be responsible for the effect, because, although some patients remained in bed during the early stages of jaundice, most of them, freed from pain during jaundice, were from the onset of jaundice not less active but more active than ever, as their statements indicate.

Counterirritation—It has been suggested that jaundice provided a form of counterirritation, that the patients were too sick with jaundice to notice the joints. On the contrary, most of them noticed the joints particularly, by reason of the degree of articular relief obtained.

Dehydration—Dehydration is said to afford some relief to the patient who has chronic arthritis.²² I do not believe dehydration was responsible for the phenomenon of relief. Dehydration was generally not noticeable. Indeed, a large amount of fluid was generally given, not because the patients were dehydrated but to combat toxicity, and analgesia continued in spite of this.

SPECULATIONS CONCERNING THE MECHANISM WHEREBY THE AGENT MAY ACT

Assuming that the responsible agent is a specific chemical substance or a combination of substances and not a nonspecific set of circumstances, it may be suggested that the phenomenon results from (1) the correction of some chemical deficiency, (2) the correction of some chemical oversufficiency or (3) a process of bacteriolysis, bacteriostasis or detoxification.

1 As has been mentioned, it is an attractive idea that jaundice provides to the general circulation and to the tissues involved in arthritis a normal chemical constituent, not an abnormal product, adequate amounts of which patients with arthritis or fibrosis did not previously possess. The validity of this idea remains to be proved.

2 Another working hypothesis might be based on a contrary point of view. Damage to the liver may temporarily interfere with the production of some substance of which the rheumatic patient has a pathologic oversupply. Thus, the hepatitis with jaundice may correct some hyperfunctioning, not hypofunctioning, state. If this were so, should not severe hepatitis alone, without jaundice, be able to invoke the phenomenon? As noted in my first report, the phenomenon did not appear in one case (case 17) in which marked cinchophen hepatitis developed without jaundice.

3 A third hypothesis is that "substance x" may have a power of detoxification or a bacteriolytic or bacteriostatic effect on organisms responsible for chronic rheumatism. Bile in certain concentrations is bacteriolytic to pneumococci, and it has recently been suggested²³ that

²² Scull, C. W., and Pemberton, Ralph. The Influence of Dietetic and Other Factors on the Swelling of Tissues in Arthritis. Preliminary Report, *Ann Int Med* 8:1247-1265 (April) 1935.

²³ Najib-Farah. Defensive Role of Bilirubinaemia in Pneumococcal Infection, *Lancet* 1:505-506 (Feb. 22) 1937.

the jaundice seen in certain cases of pneumonia represents a protective mechanism. As applied to pneumonia, the idea seems more ingenious than sound, in the absence of data indicating that patients who have pneumonia and in whom jaundice develops recover more readily than nonjaundiced patients who have pneumonia. Suffice it to say, the bacteriologists among my colleagues, carrying on certain preliminary investigations, have failed to note bacteriolysis or bacteriostasis for various athiotropic, neurotropic or neuromyotropic streptococci *in vitro* although they have used concentrations of bilirubin and bile acids, alone and separately, equal to or greater than the concentrations present in clinical jaundice. Nor have they noted definite increases in streptococcal antibodies in a few of the cases of jaundice accompanying arthritis. Furthermore, several of the jaundiced arthritic patients obviously had not been "sterilized" of their athiotropic streptococci, for these organisms still could be isolated from the nasopharynx or other foci, even in the presence of the phenomenon. Further speculation is useless at present and I have no idea which theory of the cause of arthritis or fibrositis these investigations will support.

THERAPEUTIC IMPLICATIONS

The therapeutic implications of this phenomenon seem obvious. An intensive study of it may lead to a better understanding of the pathogenesis of rheumatic diseases and perhaps of the general mechanisms of immunity, or, more important, it may lead to a method of "curing" these diseases or at least of controlling their activity. Jaundice, obviously, provides not a cure but a temporary control, at least, of symptoms. But is it not likely that the differences between a preliminary temporary remission and the final permanent remission or cure are merely quantitative—differences of degree and of persistence? As has been stated before, it would be gratifying if one were able to repeat nature's dramatic (if accidental) method of control, to induce at will, repeatedly if necessary, a similar remission of symptoms by the use of some non-toxic accompaniment of jaundice effective in available concentrations.

ATTEMPTS TO REPRODUCE THE PHENOMENON

In attempting to reproduce the phenomenon for research on the treatment of arthritic patients, various methods of approach were considered. It was decided to administer to patients who wished to cooperate in the investigation the different available constituents of bile, first alone and then in combination, first by the simplest routes (oral and rectal) and later intravenously or otherwise. Because of the cost and relative unavailability of bilirubin at the time the investigation was under way other substances were used first.

Bile Salts—A number of essentially similar preparations are available. One preparation²⁴ was given by mouth in doses up to 112 tablets (total 224 grains [14.6 Gm]) in fourteen days. Ox bile was given in doses up to 890 grains (57.8 Gm) in thirteen days. These are equal to or above the usual doses prescribed. The results were questionable. Some arthritic patients felt partially relieved, others were unaffected. Obviously the complete phenomenon provided by spontaneous jaundice was not being reproduced by these small doses of bile salts. Rather than persist in their use it was decided to postpone further investigations with them and to progress to other methods in an attempt to obtain the full effect comparable to the phenomenon described, not the slow, indefinite type of improvement which current methods already provided.

Synthetic Bile Salts—The sodium salt of dehydrocholic acid (decholin sodium) was administered intravenously, by mouth and in combination. One ampule (2 Gm) was given to each of several patients with arthritis or with fibrositis intravenously daily for from eight to twenty-one days. The tablets, each of $3\frac{3}{4}$ grains (0.25 Gm), were given orally in doses up to a total of 178 tablets (667.5 grains [44.5 Gm]) in twenty-one days. Decholin was given by Lebermann²⁵ to one patient with acute articular rheumatism, with reported benefit. It has also been used by others in the study of the hepatic function of patients with chronic arthritis.²⁶ The results noted by my patients were variable in the main, being negative. Some believed their pains were partially relieved, but, as with the previous preparation, it seemed evident that the ordinary doses of this preparation given alone would not precipitate the complete phenomenon. This was also the tentative conclusion of Sidel.²⁷

Diluted Ox Bile—Variable amounts of sterile ox bile diluted in water and olive oil were administered by proctoclysis but proved irritating and were promptly evacuated.

Human Bile—It was frankly believed that administration of bile or its constituents by the oral or by the rectal route would be of no therapeutic value, since administration of bile products by these routes could not be expected to increase materially their concentration in the general blood stream. The administered substances, if absorbed, probably would pass only through the enterohepatic circulation and would

24 The preparation used was glychotauro, which is manufactured by Hynson, Westcott & Dunning, Baltimore.

25 Lebermann, Ferdinand. Klinische Erfahrungen mit "Decholin," Fortschr d Med **44** 703-704 (July) 1926.

26 Rawls, W. B. Liver Function in Rheumatoid (Chronic Infectious) Arthritis. Preliminary Report, Ann Int Med **10** 1021-1027 (Jan) 1937.

27 Sidel, Nathan. Personal communication to the author.

never reach the general (or articular) circulation. Nevertheless, Dr Winfield Butsch procured a fairly large quantity of human bile which had drained from a T tube and which was free from pathogenic organisms and administered it to a few of my arthritic patients. Amounts of human bile up to 2,600 cc in one day (7,650 cc in ten days) were given by stomach tube. The concentration of serum bilirubin was not increased, and relief from articular symptoms was not noted. Contrary to expectation, these amounts of "heterologous bile" did not produce any gastro-intestinal symptoms. Indeed, one patient took it with pleasure, saying it increased his appetite.

Liver Extract—Occasionally I have used commercial preparations of liver extract in the treatment of arthritic patients with secondary or with coincident pernicious anemia. The use of such preparations in ordinary amounts seemed to have no marked effect on articular symptoms, certainly none similar to the phenomenon characteristic of spontaneous jaundice. This also has been the experience of Dr George Minot²⁸ and of Dr William Murphy²⁹. Therefore, this method of approach has not been extensively repeated.

Transfusions of Highly Jaundiced Blood—In the hope that "substance x" might be present in potent amounts in portions of jaundiced blood available for transfusion, four arthritic patients were given from one to four such transfusions. To my knowledge, jaundiced blood has not heretofore been deliberately used for transfusion. Because Dr Lundy and I were uncertain of its effects, small doses were first given, and only persons of identical blood groups were used as donor and recipient. What I called round-robin transfusions were arranged. Non-arthritic jaundiced patients, suffering from a variety of hepatic disorders, whose blood showed a negative Wassermann reaction and was sterile, were willing to cooperate, giving an amount of their "bad blood" for twice as much "good blood" from a healthy professional donor, at no expense to the patients. The jaundiced blood was injected into non-jaundiced arthritic patients in the usual manner. One patient, for her fourth transfusion, received 800 cc of jaundiced blood, the concentration of serum bilirubin being 21 mg per hundred cubic centimeters. Thus, only a relatively small amount of bilirubin was actually injected, namely, 168 mg. In general, there was no reaction or only the usual slight reaction, as from any transfusion. During the completion of this large transfusion, extensive hives developed, and there was a distinctly yellow tinge to the skin. The next day she insisted she had less pain, if so, relief was transient, and the serum bilirubin content was slightly but not materially, increased.

28 Minot, George. Personal communication to the author.

29 Murphy, William P. Personal communication to the author.

Artificially Produced Jaundice—Obviously, other methods of approach were necessary if an adequate amount of the hypothetic agent was to be provided. Methods of inducing relatively harmless jaundice were sought. Single doses of as much as 500 mg of bilirubin, injected intravenously, are excreted rapidly and are (or were) expensive³⁰ and ineffective. Both cinchophen and neoarsphenamine produce jaundice inconsistently, they are not controllable in their effect and their use may have serious consequences. Simple catarrhal jaundice does not seem subject to experimental reproduction. The tropical types of jaundice are dangerous or unsuitable.

In spite of all difficulties, it became evident that a reproducible, relatively harmless type of jaundice was required in order to study the phenomenon adequately. A poor mosaic was being provided by the patchwork chemical investigations accomplished with the cooperation of patients who had spontaneous jaundice, none of them lived near Rochester, so they usually had to go home just when desirable chemical studies were being made. Chemical analyses made on samples of their blood mailed to the clinic were of uncertain value. To study the intricacies of the phenomenon, one should study the changing physiologic and chemical processes in different phases: before the period of jaundice, in the preicteric stage, as jaundice becomes visible and the phenomenon becomes apparent, as jaundice fades and disappears but analgesia persists, and finally when reactivation of the disease occurs.

Toluylenediamine Jaundice—The studies of Wolff,³¹ McGowan,³² and McGowan, Bollman and Mann³³ suggested that toluylenediamine might be a suitable substance to use in the first attempts deliberately to induce jaundice in a volunteer arthritic patient. Toluylenediamine jaundice in animals was intense, it was somewhat controllable, it was of intrahepatic type, and after jaundice had disappeared the results of hepatic function tests returned to normal, and there was no pathologic evidence of significant damage to the liver. Recognizing the possible risk, a discouraged arthritic patient (fig 3), thoroughly disgusted with results she had obtained from an amazingly long series of orthodox, and unorthodox, measures employed over a period of thirteen years, elected to take toluylenediamine orally (June 1936). I was particularly fortunate in

30 At the time the work was being done the cost was \$25 a gram.

31 Wolff, H. J. The Physiologic Action of Toluylenediamine and Its Relation to Experimental Jaundice, *J. Pharmacol. & Exper. Therap.* **50** 407-419 (April) 1934.

32 McGowan, J. M. Bile Salts in Toluylenediamine Jaundice, *Proc. Staff Meet., Mayo Clin.* **10** 565-567 (Sept 4) 1935.

33 McGowan, J. M., Bollman, J. L., and Mann, F. C. The Bile Acids in Icterus Produced by Toluylenediamine, *J. Pharmacol. & Exper. Therap.* **58** 305-311 (Nov) 1936.

the selection of this patient, because annoying gastro-intestinal irritation was induced, only slight jaundice was obtained (and that with some difficulty) and the jaundice was ineffectual against the pain. Nevertheless, the woman cooperated remarkably and accepted the failure philosophically. The details of this case will be reported separately in another paper.

Contrary to expectation, the jaundice induced was wholly of the hemolytic type. With extreme caution the patient was carried to an erythrocyte count as low as 1,530,000 per cubic millimeter of blood and to a concentration of hemoglobin of 5.2 Gm per hundred cubic centimeters. The color of the eyes and skin was lemon, not orange, the jaundice was transient and rather mild, and the maximal concentration of serum bilirubin was only 6.3 mg (direct reaction), never entering

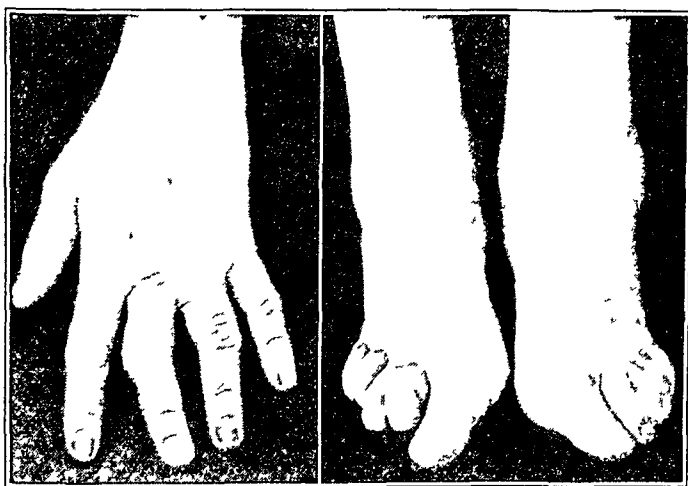


Fig. 3—One hand and both feet of a patient who had had severe chronic infectious arthritis for thirteen years. One may note deformities of the fingers and toes and swelling of the ankles, especially of the left ankle. Mild "experimental jaundice," which was induced with toluylenediamine, was not associated with remission of articular symptoms.

the "zone of therapeutic effectiveness." Subsequently, two transfusions and other hematonics were given, and the woman made a rapid and uneventful recovery as far as the blood was concerned. Results of tests showed that the hepatic and renal functions either were normal or had returned promptly to normal.

Some more feasible method of studying the phenomenon, a method perhaps adaptable to the field of therapy, is needed, but when it is obtained it should not be regarded as an end but only as a means to an end. Therapeutic jaundice may be an attractive term, but even if successfully induced, it should be, at best, considered a crude form of treatment, just a step—but an important one—on the way to the refined therapy of the future.

SUMMARY AND CONCLUSIONS

Further observations have been made on the analgesic or the inactivating effect of jaundice on chronic infectious (atrophic, rheumatoid) arthritis, on primary fibrositis and on certain types of lumbosacral and sciatic pain. Clinical and chemical studies have been made on a new series of thirty-one patients whose rheumatic symptoms were partially or, generally, completely relieved coincident with the onset of spontaneous jaundice. With the addition of the fourteen patients reported on in the first series, a total of forty-five patients have experienced this phenomenon: twenty-eight with chronic infectious (atrophic) arthritis, twelve with primary periarticular and intramuscular fibrositis, four with lumbosacral or sciatic pain and one with hypertrophic arthritis localized in the hip joints. Various types of jaundice appeared to be equally effective: intrahepatic jaundice from cinchophen, spontaneous intrahepatic jaundice of the catarrhal or epidemic infectious type, intrahepatic jaundice associated with hepatitis and cirrhosis, and obstructive jaundice from stones or from a malignant growth. No opportunity to study the effect of marked hemolytic jaundice has presented itself.

The phenomenon was dependent more on the quantity than on the quality of jaundice. The concentration of serum bilirubin served as a general index of the effectiveness of the phenomenon, and what I have called the zone of therapeutic effectiveness has been established tentatively as beginning at a concentration of serum bilirubin of about 8 to 10 mg. per hundred cubic centimeters. However, certain data are at hand which suggest that the concentration of bilirubin in jaundice may not be the chief or sole factor in producing the phenomenon.

The phenomenon was characterized by the dramatic promptness of its appearance, its notable obviousness and the completeness of its effect. The duration of the remissions induced by jaundice bore a general but not a specific relation to the intensity and duration of the coincident jaundice. The analgesic effect of jaundice was noted generally within the first three days of visible jaundice. Of the thirty-one new patients who experienced analgesia, twenty-two (71 per cent) received complete relief and nine (29 per cent) received partial but almost complete relief. All nine patients with fibrositis and 63 per cent (twelve) of the nineteen arthritic patients were relieved completely although temporarily, of all rheumatic symptoms.

Significant jaundice precipitated a remission, apparently not a cure, of the diseases under consideration, but the remissions provided "vacations from rheumatism" which were gratefully received by the patients, most of whom would have preferred to make permanent the trade of the new condition for the old. The remission of articular and muscular symptoms lasted from three weeks to forty-five months, in general they lasted several weeks. The arthritic patients were relieved of symptoms

for an average of about four months, and the patients with fibrositis, for an average of about five months. The remissions lasted roughly about twice as long as the jaundice, but because of variable factors, this is a generalization not applicable to individual cases.

In the majority of cases the rheumatic symptoms returned to their previous intensity, but in 42 per cent of the cases the symptoms recurred in milder form and have so remained.

A study of thirteen additional new patients (four with atrophic arthritis and nine with articular or neuritic symptoms resulting from conditions other than atrophic arthritis or primary fibrositis) who did not experience analgesia in the presence of jaundice of varying intensity indicated the relative specificity of the reaction and its closer relation to the quantity than to the quality of jaundice. Painful gouty arthritis, post-herpetic neuralgia, ischemic neuritis, juxta-articular metastasis and arthralgia of a special type were unrelieved in the presence of jaundice which at times reached the so-called zone of therapeutic effectiveness.

The therapeutic implications are obvious. The responsible agent and the mechanism whereby it acts are as yet unknown. Some working hypotheses have been developed. Attempts to reproduce the phenomenon, for investigative rather than for immediate therapeutic purposes, were made. They included the administration of whole bile and certain of its constituents by various routes. Natural and synthetic bile salts (decholin) were given. Bile was fed by stomach tube. Transfusions of deeply jaundiced blood were tried. Jaundice was produced by the administration of toluylenediamine. The clinical and chemical results of these methods were studied, by these means and with the rather small doses used, the phenomenon has not yet been reproduced.

For an adequate study of the phenomenon, the development of a method to produce suitable artificial jaundice may be required. However, when it is accomplished, artificial or "therapeutic" jaundice should be regarded not as an end in itself but only as a means to an end. Two conclusions seem permissible.

- 1 Chronic infectious (atrophic, rheumatoid) arthritis and primary fibrositis are not necessarily relentless, uncontrollable diseases. Their pathologic physiology is more completely and more rapidly reversible than has been supposed heretofore.

- 2 Nature possesses a highly effective method of quickly stopping the disease for a while and of producing a dramatic remission, this phenomenon is precipitated more rapidly and more completely by jaundice than by any other known physiologic change or therapeutic method. It behooves physicians to discover this antidote and the mechanism of its action.

The discussion of this paper appears in conjunction with that of the following paper, by Drs. Thompson and Wyatt.

EXPERIMENTALLY INDUCED JAUNDICE (HYPERBILIRUBINEMIA)

REPORT OF ANIMAL EXPERIMENTATION AND OF THE PHYSIOLOGIC
EFFECT OF JAUNDICE IN PATIENTS WITH ATROPHIC
ARTHRITIS

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Since the publication of the article by Hench,¹ in 1933, in which it was noted that intercurrent jaundice may evoke a remission of chronic atrophic arthritis and fibrositis, we have been actively interested in the experimental production of jaundice. The observations of Hench have been confirmed by Sidel and Abrams² and by Hench³. We have studied three patients with atrophic arthritis in whom jaundice occurred. Jaundice occurred in two of these patients after toxic hepatitis, in one case due to neocinchophen (30 grains [2 Gm] daily for sixteen days) and in the other case to neocinchophen (12 grains [0.8 Gm] daily for twenty-four days) and oxo-ate B (calcium ortho-iodoxybenzoate, 15 grains [1 Gm] daily for twenty days). In one patient no effect on the arthritis was noted (the serum bilirubin content was not determined), but the other patient, with the onset of jaundice, was relieved of pain. During the jaundice, which lasted thirty days, the articular symptoms were entirely relieved. The serum bilirubin level for this patient was 24 mg per hundred cubic centimeters. With the disappearance of the jaundice the pain returned slightly, however, she continued fairly free from manifestations for three years. The arthritis then returned with

Presented in part before the Fifth Conference on Rheumatic Disease held by the American Rheumatism Association Atlantic City, N J, June 7, 1937

1 Hench, P S. Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis and Sciatic Pain, Proc Staff Meet, Mayo Clin 8 430 (July 12) 1933

2 Sidel, N, and Abrams, M I. Jaundice in Arthritis. Its Analgesic Action, New England J Med 210 181 (Jan 25) 1934

3 Hench, P S. The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, Ann Int Med 7 1278, 1934. A Clinic on Some Diseases of the Joints. IV The Inactivating Effect of Jaundice in Chronic (Infectious) Arthritis and Fibrositis, M Clin North America 19 573, 1935

severity The third patient (referred by Dr R A Hicks) was a girl aged $3\frac{1}{2}$ years Nine months previously, severe polyarticular arthritis of the atrophic type developed The joints of the fingers, wrists, elbows, knees, ankles and neck were involved, with marked limitation of motion, heat, swelling and pain Five blood transfusions of 275 cc each were given in five weeks After the last transfusion a severe reaction occurred, with chills and repeated emesis at three to four hour intervals for twelve hours Jaundice appeared the following morning (grade 3+, serum bilirubin content, 12 mg) and persisted for approximately five days Hemoglobinuria appeared and remained for three days after the reaction With the onset of jaundice the swelling and pain diminished, the arthritis completely disappeared and the child remained well for sixteen months after which the symptoms returned with less severity

This case is of interest because the jaundice was accompanied with a severe posttransfusion reaction, marked destruction of red blood cells and hemoglobinuria Although it may be questionable whether this was hemolytic jaundice, the case is included here because the jaundice was followed by a remission of the arthritis

Bile contains four main components ⁴ (1) bile pigments, (2) bile salts, (3) lipid constituents and (4) mucin It has been generally observed ⁵ that of this group, the bile pigments alone reach relatively higher levels in the circulation in jaundice of the hemolytic type and that both bilirubin and bile salts show higher levels in jaundice of the obstructive and toxic type Although the majority of the instances reported in the literature indicate that in the cases of jaundice in which the most beneficial effect was noted there was an accompanying rise in the levels for serum bilirubin and bile salts, these two substances cannot be considered entirely responsible, since we have observed a remission following jaundice (third case) in which the level of bile salts presumably was not raised Hence, we determined the effects of bile pigments alone of bile salts alone and of bile pigments and bile salts in combination There was no apparent reason for determining the effect of the other constituents of bile, as they are not involved We have observed that the serum bilirubin levels ⁶ are lower for patients with

4 Wright, S Applied Physiology, ed 4, New York Oxford University Press, 1932, p 418

5 Hawk, P B, and Bergem O Practical Physiological Chemistry, ed 10, Philadelphia, P Blakiston's Son & Co, 1931

6 The method of Ernst and Forster gives higher values than the quantitative van den Bergh test, as the comparison of colors is direct and measures other pigments as well as bilirubin Ernst, Z and Forster, J Ueber die Bestimmung des Blutbilirubins, Klin Wchnschr 3 2386, 1924

chronic atrophic arthritis than for normal persons (table 1) These findings confirm the observations made by Race⁷

We studied the effect of single and of repeated intravenous injections of bilirubin at various levels of dosage in rabbits The results may be briefly summarized as follows 1 Bilirubin was rapidly excreted after single intravenous injections 2 Repeated injections of 20 mg of bilirubin per kilogram of body weight daily for ten days produced chronic bilirubinemia and retention of the pigment in the tissue 3 No

TABLE 1—*Serum Bilirubin Values* for Patients with Chronic Atrophic Arthritis and for Normal Persons*

Patients With Chronic Atrophic Arthritis			Normal Persons	
Number	Red Blood Cells, Millions per Cu Mm	Serum Bilirubin, Mg per 100 Cc	Number	Serum Bilirubin, Mg per 100 Cc
1	4.20	0.36	1	2.06
2	4.10	1.58	2	2.07
3	4.85	1.63	3	2.76
4	4.80	1.50	4	1.98
5†	4.50	2.24	5	1.72
6	4.40	1.70	6	1.70
7	4.38	1.69	7	1.84
8	4.01	1.70	8	2.39
9	4.85	1.78	9	2.07
10	4.50	1.04	10	2.22
11	4.08	2.01	11	2.51
12	4.79	1.66	12	2.25
13	4.82	1.69	13	2.10
14	4.60	1.60	14	1.91
15	4.06	1.56	15	2.10
16	4.50	1.50	16	1.99
17	4.53	1.67	17	1.91
18	4.51	0.88	18	1.99
19	4.68	0.90	19	2.05
20	4.35	1.10	20	2.08
21	4.54	0.67	21	1.94
22	4.60	0.63	22	1.98
23	4.55	0.94	23	2.03
24	4.79	1.50	24	1.89
25	4.61	1.28	25	2.60
Averages		1.39		2.06

* The Ernst Forster method was used

† This patient had chronic atrophic arthritis and coronary thrombosis

toxic effects were noted during the administration or at autopsy 4 The single fatal dose of bilirubin was 175 to 200 mg per kilogram These findings indicated that the excretion of bilirubin was rapid, even with repeated doses but that the tissue took up sufficient pigment so that slight bilirubinemia persisted

Three patients with chronic atrophic arthritis were given a series of repeated injections of bilirubin in doses of 10 to 15 mg per kilogram daily Observations on these patients demonstrated that bilirubin is rapidly but not completely excreted from the blood after repeated injec-

7 Race, J Biochemical Investigations in Chronic Rheumatic Diseases, in Report on Chronic Rheumatic Diseases London, H K Lewis & Co., Ltd, 1935, no 1, p 61

tions Slight hyperbilirubinemia developed, and there was sufficient retention in the tissues to produce icterus (table 2 and chart 1) Little or no symptomatic improvement was noted in this group

It should be mentioned here that many investigators⁸ have injected bilirubin into patients as a test of hepatic function or for other purposes, but no mention has been made of the effect of this substance on the symptoms of atrophic arthritis

We then tried the administration of bile salt alone (decholin sodium) to ten patients with chronic atrophic arthritis They were given intravenously 2 Gm of the salt daily for nine to twelve days Little or no symptomatic improvement was noted This is confirmatory of the results of Hench⁹

The next step was the employment of bilirubin and bile salt together

The animal experiments were repeated, using bilirubin at 20 mg per kilogram and the sodium salt of dehydrocholic acid¹⁰ in doses of 40 mg

8 (a) von Bergmann, G Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, *Klin Wchnschr* **6** 776, 1927 (b) Eilbott W Funktionsprufung der Leber mittels Bilirubinbelastung, *Ztschr f klin Med* **106** 529, 1927 (c) Harrop, G A, Jr, and Barron, E S G The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, *J Clin Investigation* **9** 577, 1931 (d) Soffer, L J Bilirubin as a Test for Liver Function During Normal Pregnancy, *Bull Johns Hopkins Hosp* **52** 365, 1933 (e) Soffer, L J, and Paulson, M Residual Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, *Arch Int Med* **53** 809 (June) 1934 (f) Rosenthal, S M Modern Methods of Testing Liver Function, *M Ann District of Columbia* **1** 294, 1932 (g) Ruhbaum, W N, and Matheja, W Leberfunktionsproben bei latenter Leberschadigung, *Klin Wchnschr* **14** 1568, 1935 (h) Fulde, W Wert und Methodik verschiedener Leberfunktionsprufungen fur Klinik und Praxis, *ibid* **14** 1201, 1935 (i) Kalk, H Klinische Untersuchungen uber die Frage des latenten Leberschadens, *Deutsche med Wchnschr* **58** 1078, 1119 and 1160, 1932 (j) Dragstedt, C A, and Mills, M A Bilirubinaemia and Bromsulphalein Retention, *Proc Soc Exper Biol & Med* **34** 467, 1936 (k) Takane, S Ueber den Einfluss verschiedener Narkosemittel auf die Leberfunktion Experimentelle Untersuchungen mit Bilirubin und Kongorot, *Arch f klin Chir* **170** 672, 1932 (l) Scholderer, H Disappearance of Injected Bilirubin from Blood Stream, in Cameron, A T, and Gilmour, C R The Biochemistry of Medicine, London, J & A Churchill, 1933 (m) Rabnowitch, I M Renal Threshold of Bilirubin, *J Biol Chem* **97** 163, 1932 (n) Saiki, Sanetosshi Experimental Investigation on the Fate of Bilirubin Introduced into the Blood Vessels, *Jap J Gastroenterol* **2** 203, 1930, **3** 1, 119, 123, 192, 195, 197 and 203, 1931 (o) Marengo, G, and Massimello, F Der Einfluss der Tachidrolol-Decholin-Mischspritze auf die Bilirubinamie und die Diurese, *Arch f exper Path u Pharmakol* **178** 486, 1935 (p) Greene, C H, and Snell, A M Studies in the Metabolism of the Bile, *J Biol Chem* **78** 691, 1928 (q) Elliott, C A, and Nadler, W H Diseases of the Liver, in Tice, F Practice of Medicine, Hagerstown, Md, W F Prior Company, Inc, 1921, vol 7, p 80

9 Hench, P S Personal communication to the authors

10 Decholin sodium was obtained from Riedel-de Haen, Inc, New York

TABLE 2—Serum Bilirubin Values After Repeated Intravenous Injections of Bilirubin Alone

Case No	Normal Value	Serum Bilirubin, Mg per 100 Cc *																	
		1 Injection		2 Injections		3 Injections		4 Injections		5 Injections		6 Injections		After Last Injection					
		5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	5 Min Inter-val	24 Hr Inter-val	2 Days	4 Days	7 Days	15 Days
1	0.83	10.73	0.99	8.43	0.89	15.12†	1.93	12.00	2.59	15.1	2.51	2.38	5.34‡	2.83		2.60	2.10	1.30	
2	0.67	11.96	1.83	13.16	2.11			11.71	3.37							2.21	2.00	1.50	1.00
3	0.63	12.15	1.01	12.00	1.39											2.52	1.80	0.98	

* The Ernst Forster method was used
† The dose employed was 15 mg per kilogram
‡ The dose employed was 5 mg per kilogram

per kilogram This bile salt was selected as it is apparently less toxic intravenously than some other bile salts¹¹ In addition to the previous research, we studied the functional capacity of the liver (biom-sulphalein test)

A brief summary of this study is as follows 1 In single doses the clearance of bilirubin was essentially the same with bile salt as with bilirubin used alone 2 With repeated administration there appeared a slightly greater retention of pigment in the blood and tissues when bile salt was added to the bilirubin 3 No evidences of toxicity appeared during or after the administration or at autopsy

A patient having chronic nonspecific atrophic arthritis was selected He was given daily doses of 10 mg of bilirubin per kilogram intravenously for four days, and on the fifth, sixth and seventh days 40 mg of decholin sodium per kilogram was added to the infusion This was

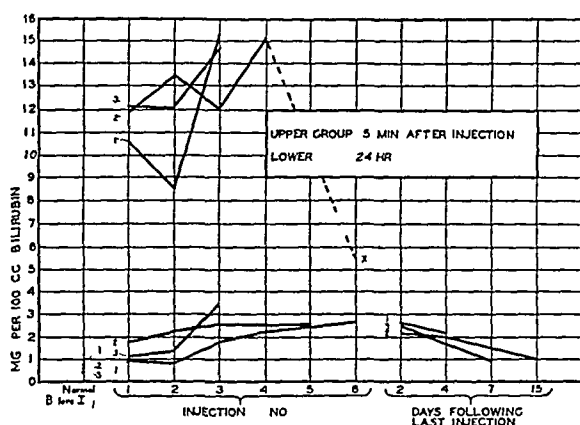


Chart 1—The clearance of bilirubin from the blood stream after repeated injections of bilirubin (10 mg per kilogram) X indicates 5 mg and X 15 mg of bilirubin per kilogram

done in order to contrast the effects of bilirubin alone with the effects of bilirubin and bile salt combined After four injections of bilirubin, slight icterus developed, but no relief of symptoms was noted, both knees and one ankle remaining warm, swollen and painful However, within eight hours after the fifth infusion (bilirubin and bile salt) marked relief from pain in all the involved joints appeared He stated that for the first time in six months he had slept entirely through the night without being awakened by pain In addition, the swelling of the joints had diminished slightly, and he was more icteric The serum

11 Weigand F A Diuretic Action of Intravenous Sodium Dehydrocholate J A M A 105 2034 (Dec 21) 1935 Steiner, R F, Bartle, H J and Lyon B B V The Chologogue Effect of the Intravenous Injection of Sodium Dehydrocholate with a Resume of the Literature on Bile Salt Metabolism, Am J M Sc 182 822, 1931

bilirubin content twenty-four hours after this infusion was 2.81 mg per hundred cubic centimeters (chart 2, case 1). The van den Beigh reaction was indirect. After the two succeeding injections the articular swelling rapidly diminished, and the analgesia has persisted up to the time of writing (five months). This reversal of symptoms came on so dramatically and suddenly that one immediately notes the similarity between this case and the reported cases of analgesia occurring clinically with jaundice.

Again, for purposes of contrast, the mixture of bile salt and bilirubin was given to a patient who had previously received bilirubin alone without beneficial effect on the arthritis. The first infusion of bilirubin and bile salt, in a ratio of 10 mg to 40 mg, respectively, per kilogram, was followed within eight hours by relief of pain. The patient stated the

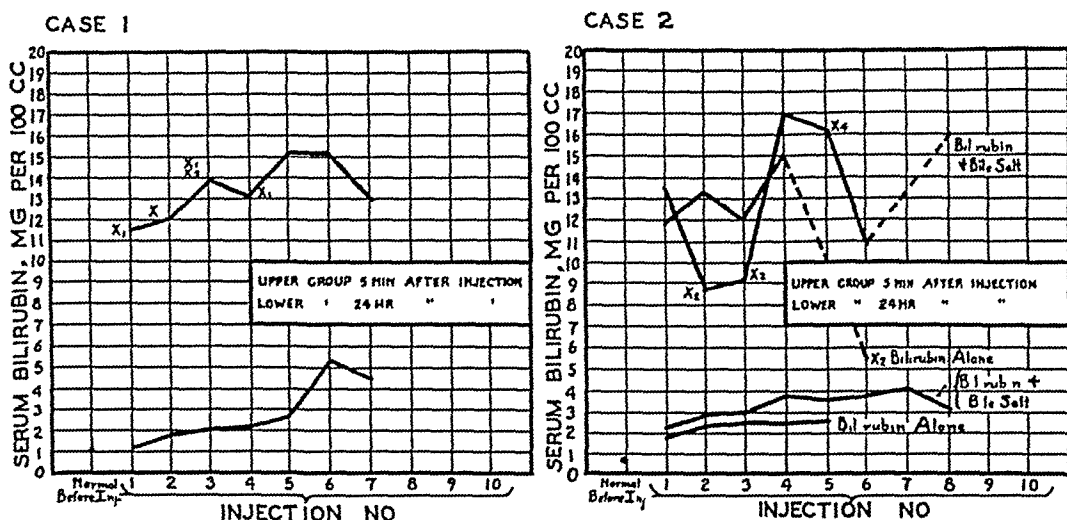


Chart 2—Case 1 shows the clearance of bilirubin alone and the effect of adding bile salt. The dose was 10 mg of bilirubin and 40 mg of bile salt per kilogram, X₁ indicates that bile salt was not used in the injection. X indicates a dose of 15 mg of bilirubin per kilogram. Case 2 shows the clearance of bilirubin after intravenous injections of bilirubin alone and of bilirubin and bile salt (same patient). X₂ indicates a dose of 5 mg and X₄, a dose of 20 mg of bilirubin per kilogram.

next day, 'I stepped out of bed this morning, and my feet and hands felt as though I never had had arthritis.' The scleras were icteric. The swelling had subsided somewhat, and none of the involved joints were painful. The serum bilirubin level at twenty-four hours was 2.4 mg per hundred cubic centimeters (chart 2, case 2). A second and a third infusion were given, only 5 mg of bilirubin and 40 mg of bile salt per kilogram being used. After these two infusions there was some pain in the joints, and, as he said, 'the results were not nearly as good as on the first day.' For the fourth injection there was a 10 to 40 mg per kilo-

gram ratio of bilirubin to bile salt, and this resulted in complete analgesia. The fifth injection contained 20 mg of bilirubin and 40 mg of bile salt. The sixth, seventh and final injections employed 10 mg of bilirubin and 40 mg of bile salt per kilogram. The patient stated that the joints were better than they had been for a year. The swelling had diminished, pain had disappeared and he was definitely icteric. The serum bilirubin level was 3.12 mg per hundred cubic centimeters. This remission lasted three weeks, at which time the pain and swelling returned as before the administration. This case indicates some correlation between the serum bilirubin level and the analgesia, i. e., when 10 mg of bilirubin (and bile salt) per kilogram was given, it produced a theoretical rise in the serum bilirubin level of 14 mg per hundred cubic centimeters, with resulting analgesia, but 5 mg of bilirubin per kilogram, producing a theoretical rise in the serum bilirubin level of 7 mg per hundred cubic centimeters, did not result in analgesia. This observation also indicated that since there was apparently an analgesic serum bilirubin level, each dose should reach this or a slightly higher level. Hence, in the succeeding cases this dosage was employed unless for experimental or other reasons it was altered.

The combination of bilirubin and bile salt was then given to eight patients with chronic atrophic arthritis. A summary of the data for these patients is tabulated in table 3. The two cases just cited are included in the summary.

Briefly, the observations are as follows. Of ten patients, three received seven, two, eight, three, nine, one, ten, and one, eleven daily infusions of bilirubin and bile salt. The first observable icterus in the eyes was noted after the first to the fourth injection. This became generalized after two to eight injections. However, varying degrees of intensity were noted, as a general rule the icterus became progressively more marked with each succeeding injection. The observable jaundice disappeared from fourteen to twenty-three days after the last administration. A diminution of the swelling was noted after one to nine infusions. Analgesia was noted after one to seven injections and persisted for varying intervals, the shortest period being twelve days. The longest period cannot be determined as five patients have had no return of pain up to the time of writing (elapsed intervals of five, five and one-half, two, one and one month, respectively).

The serum bilirubin levels before the administration and at five minute and twenty-four hour intervals after each injection are shown in table 4 and charts 3 to 5 (the five minute sample of blood was taken from a contralateral vein, the twenty-four hour sample was taken from a vein just previous to the injection of bilirubin and bile salt into that vein). The clearance of bilirubin from the blood stream was rapid after

Case No.	Duration of Arthritis, years	Total Number of Infusions of Bilirubin and Bile Salt Given	Icterus			Analgesia
			Onset After Infusion, Number	Duration After Infusion, Days	Duration After Infusion, Days	
1	10	Seventy				
2		Marked				

Case No	Duration of Arthritis, years	Severity	Total Number of Infusions of Bilirubin and Bile Salt Given	Icterus				Swelling	Effect and Duration
				Onset After Infusion, Number		Duration After Infusion, Days	Onset After Injection Number		
				Uyes	Skin				
1	10	Marked	7	3	5	18	1	Analgesia, diminished swelling continuing to present (5 months)	
2	3.5	Moderate	7	3	5	18	1	Analgesia, diminished swelling continuing to present (5 months)	
3	2.5	Marked	7	3	5	18	1	Analgesia, diminished swelling continuing to present (5 months)	
4	6.0	Marked	7	3	5	18	1	Analgesia, diminished swelling continuing to present (5 months)	
5	2.0	Moderate	8	1	6	21	1	Analgesia, diminished swelling continuing to present (5 months)	
6	6.5	Marked	9	2	2	18	7	Analgesia, diminished swelling continuing to present (5 months)	
7	3.0	Marked	9	1	8	21	1	Analgesia, diminished swelling continuing to present (5 months)	
8	7.0	Marked	9	2	5	23	1	Analgesia, diminished swelling continuing to present (5 months)	
9	11.0*	Moderate	8	2	1	11	9	Analgesia, diminished swelling for 12 days to present (2 months)	
10	10	Moderate	10	2	6	21	5	Analgesia, diminished swelling for 12 days to present (2 months)	
11	11	Moderate	11	2	7	20	6	Analgesia, diminished swelling for 12 days to present (2 months)	
						22	2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for 12 days to present (2 months)	
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							2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for 12 days to present (2 months)	
							2	Analgesia, diminished swelling for	

Age	Sex	Duration of disease	Duration of quiescence	Duration of relapse
11	6	21	5	2
2	7	20	2	1
22				

TABLE 4—Serum Bilirubin Values * After Repeated Intravenous Injections of Bilirubin and Bile Salts

Case No	Normal Value	Injection No 1			Injection No 2			Injection No 3			Injection No 4			Injection No 5			Injection No 6			Injection No 7			Injection No 8			Injection No 9			Injection No 10			Injection No 11		
		5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val	5 Min Inter val	5 Min val	24 Hr Inter val				
1	1.20	11.60†	1.02	12.00†	1.70	14.00†	2.10	13.80†	2.09	15.30†	2.80	15.39	3.39	13.70	4.30																			
2	0.67	13.40	2.14	8.90§	2.90	9.40§	3.00	17.00	3.90	16.29	3.70	10.75	3.90		4.10		16.00	3.12																
4	1.28	13.90	2.10	14.30	2.95	12.10	3.80	13.70	2.91	16.90	3.40	12.20	4.10	17.90	4.50																			
5	1.84	12.90	1.01	11.91	2.90	13.90	3.50	12.80	2.41	16.30	3.40																							
6	1.77	26.92	3.62	12.47	2.76	11.05		11.42	2.75	13.25	3.37	12.72	3.40	12.72	4.95	35.47	5.03	16.04	3.79															
7	1.35	13.48	3.34	10.45	3.47	10.53		11.82	2.85	11.82	2.57	12.96	3.34	12.96	4.43	32.09	3.71	14.02	3.30															
8	1.63	5.76	1.31	14.40	3.15	12.72	3.34	13.75	3.40	18.72	3.96	16.44	4.16	19.82	4.97	21.06	4.05	21.03																
9	1.77	12.47	2.98	14.10	3.83	17.28	3.55	19.26	3.75	17.28	3.87	21.74	4.74	17.73	3.86	19.25																		
10	0.94	14.31	1.41	16.85	2.90		4.57		1.83	16.50	3.96	17.90	3.57	18.87¶	3.20	¶	4.04																	
11	1.72	14.21	1.50		2.70	16.50	3.63	10.21	1.75	10.78	3.53	12.67	3.08	¶	3.15	18.26¶	4.09	16.00¶	3.77															

* The Ernst Forster method was employed. The values are given in milligrams per hundred cubic centimeters.

† Bilirubin was given alone.

‡ Bilirubin was given alone, 15 mg per kilogram.

§ The dose of bilirubin was 5 mg per kilogram.

|| The dose of bilirubin was 20 mg per kilogram.

¶ The dose of bilirubin was 15 mg per kilogram.

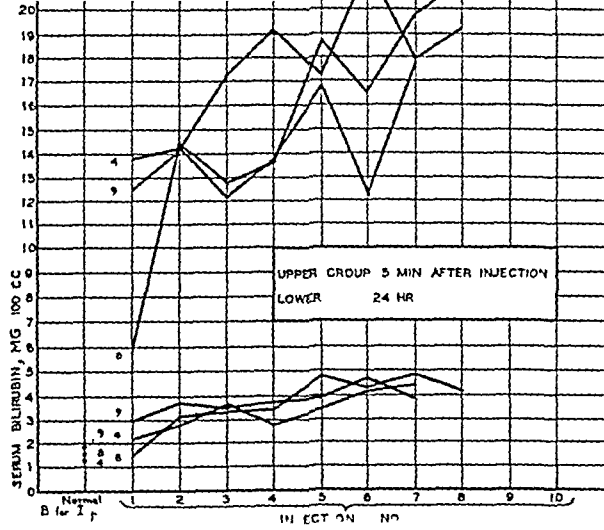


Chart 3—The clearance of bilirubin after repeated intravenous injections of bilirubin, 10 mg per kilogram, and bile salt, 40 mg per kilogram

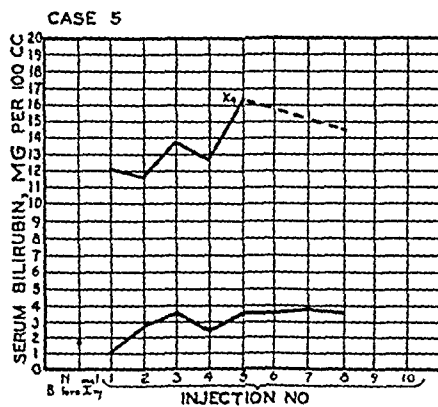
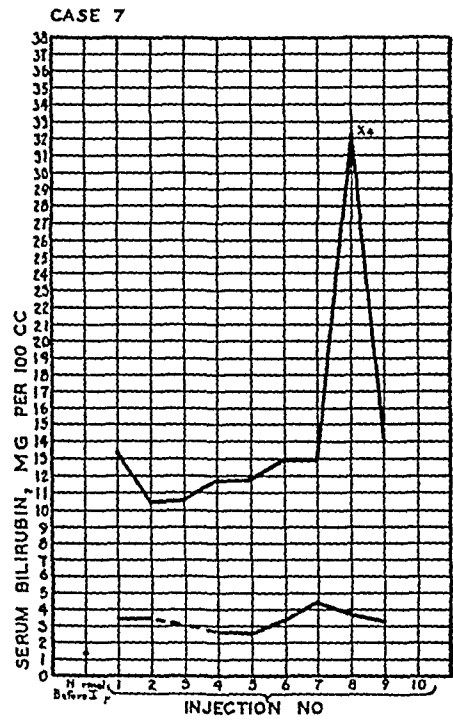
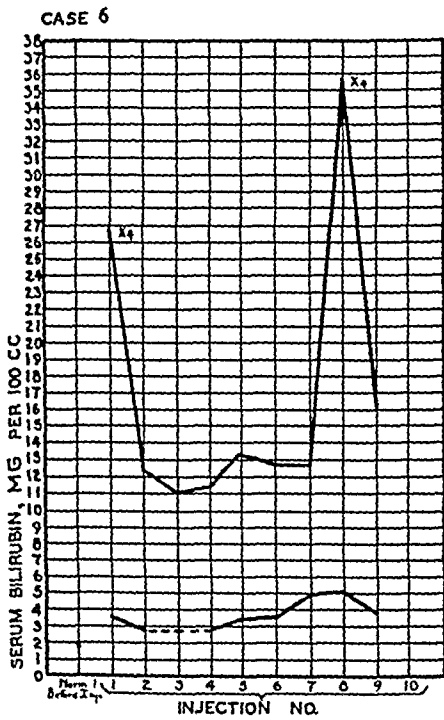


Chart 4—The clearance of bilirubin after repeated injections of bilirubin in doses of 10 or 20 (X_1) mg per kilogram with 40 mg of bile salt per kilogram. In each case the upper curve indicates values obtained five minutes after the injection and the lower curve, values obtained twenty-four hours after the injection.

both single and repeated infusions of the mixture of bilirubin and bile salt. However, after the repeated administration there was a rise in the twenty-four hour levels. Despite these low levels for bilirubin in the blood at twenty-four hours, there was sufficient retention in the tissues to produce varying degrees of icterus. The serum bilirubin appeared to be of exogenous origin, since the levels for the five minute samples approximated or were lower than the theoretical levels. The obtaining of low values at five minutes may be due to the rapid clearance of bilirubin from the blood stream.¹²

Reactions occurred in some of the patients receiving bilirubin and bile salt. From a total of eighty-five infusions, fifteen reactions appeared in six patients. Four patients had no reactions. These reactions were

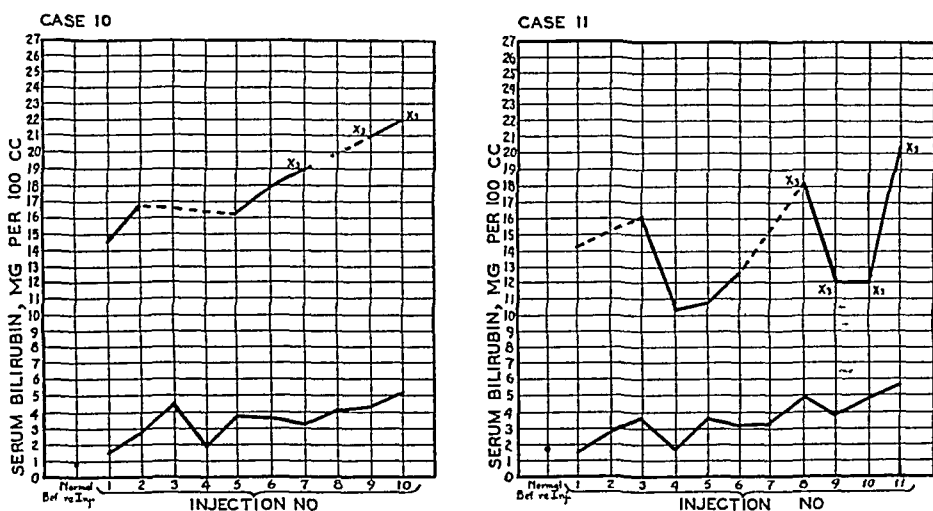


Chart 5—The clearance of bilirubin after repeated injections of bilirubin in doses of 10 or 15 (X_3) mg of bilirubin with 40 mg of bile salt per kilogram. In each case the upper curve indicates values obtained five minutes after the injection, and the lower curve, values obtained twenty-four hours after the injection.

local or general. Local reactions occurred when the same vein was used for consecutive injections. General reactions were immediate or delayed. The immediate reactions observed were flushing of the face, tachycardia and subjective sensations of fullness in the head and headache. Delayed reactions occurred one to two hours after injection and consisted of nausea, vomiting, chills, a temperature of 99 to 101 F and, subjectively, a dull ache in the back or head. All general reactions were of short duration and never appeared dangerous. The only medication required was 30 drops of aromatic spirit of ammonia, which promptly relieved the immediate general reaction. Slight diuresis occurred in these patients, and loose stools were noted occasionally.

12 Dragstedt, C. A. Personal communication to the authors.

There appeared to be no toxic effects other than the reactions. Tests of renal function (phenolsulfonphthalein) and tests of concentration and dilution (Mosenthal), as well as daily urinary examination, exhibited no evidence of renal damage before, during or after the administration. No evidence of hepatic damage (as judged by the bromsulphalein hepatic function test¹³) was revealed. In addition, the clearance of bilirubin from the blood was indicative of the functional capacity of the liver¹⁴. Additional laboratory data were obtained from complete blood counts, agglutination titers of the serum to hemolytic and green-producing streptococci, sedimentation rates (Westergren) and cultures from foci of infections. These studies were made immediately before and after the series of tests. Except for the change in sedimentation rate and the appearance of bile pigments in the urine, no noteworthy changes occurred (table 5).

Since neither bilirubin nor bile salt alone has an analgesic effect, the mechanism of their combined action is somewhat problematic. The first question that presented itself was: Is there a higher and more persistent hyperbilirubinemia when bilirubin and bile salt are used together than when bilirubin is used alone? The observations on the patients and on rabbits indicate that there is a slightly higher and more persistent hyperbilirubinemia when the two are used together than when bilirubin is used alone. However, the differences are not striking, and the clinical relief of symptoms has not been sufficiently parallel to the degree of bilirubinemia to permit one to draw any conclusions.

When we first employed this solution, we encountered several difficulties, but eventually we arrived at the following technic of preparation which has been successful in our hands.

Sufficient tenth-normal sodium carbonate for complete solution of the bilirubin (we have used 20 to 30 cc. to 0.1 Gm.) is brought to the point of boiling. The bilirubin is added, and the mixture is allowed to stand for one hour, with occasional gentle agitation. The solution is then passed through a Seitz filter. A sterile solution of bile salt is added to the filtrate. The solution is protected from the light at all times. This final solution is sterile and is administered intravenously by the gravity method directly after preparation. No difficulties have been encountered when we have prepared the solution in this manner.

CONCLUSIONS

Confirmatory of the reports of others, it was found that the administration of bile salt was without beneficial effect on the symptoms of chronic atrophic arthritis. Bilirubin alone employed similarly gave no

13 Todd, J. C., and Sanford, A. H. *Clinical Diagnosis by Laboratory Methods*, Philadelphia, W. B. Saunders Company, 1932, pp. 94 and 100.

14 von Bergmann^{8a}, Eilbott^{8b}, Harrop and Barron^{8c}.

TABLE 5—Summary of Laboratory Data Determined Immediately Before and After a Series of Intravenous Injections of Bilirubin and Bile Salt

	Blood					Focal Infection	Kidney				Liver Brom sulphalein Test, at 30 Min
	Erythrocytes, Millions per Cu Mm	Hemo globin, per Cent	Total Leuko cytes	Sedi menta tion Rate, Mm per Hr	Agglutination Titers		Urine Analysis	Phenolsulfon phthalate Test, %		Concen tration and Dilution Specific Gravity	
								1 Hr	2 Hr		
Case 1 Before	4.6	93	6,250	75	1.80	1.100	Occult red blood				
After	4.6	97	5,650	53	1.80	1.160					
Case 2 Before	4.61	91	7,000	71	Neg	Neg	Trace of albumin				
After	4.5	88	8,000	85	Neg	Neg					
Case 4 Before	4.61	91	7,000	91	Neg	Neg	Normal				No retention
After	4.6	97	7,100	29	Neg	Neg					
Case 5 Before	4.85	97	9,800	105	1.640	1.1,280	Normal				
After	4.62	93	7,700	113	1.640	1.1,280					
Case 6 Before	4.81	97	7,200	105	1.320	1.640	Normal		45	75	
After	4.72	97	6,250	15	1.320	1.640					
Case 7 Before	4.98	97	7,400	31	Neg	Neg	Normal		45	80	No retention
After	5.23	95	7,430	42	Neg	Neg					
Case 8 Before	4.91	97	8,700	61	1.640	1.1,280	Normal				
After	4.87	95	7,950	72	1.640	1.1,280					
Case 9 Before	4.58	88	7,000	63	1.320	1.320	Normal				
After	4.05	80	7,430	101	1.320	1.320					
Case 10 Before	3.92	80	7,450	60	Neg	Neg	Normal		15	80	No retention
After	3.9	80	7,150	19	Neg	Neg					
Case 11 Before	4.51	91	8,000	62	1.1,280	1.2,560	Normal		50	75	No retention
After	4.52	97	6,400	42	1.1,280	1.2,560					

beneficial effects. However, the combination of bilirubin and bile salt had an ameliorating effect on the symptoms of atrophic arthritis.

The mechanism of this action is not obvious, but it seems clear from these studies that one can produce artificial jaundice which apparently duplicates the effect observed by various workers when clinical jaundice intervenes in cases of atrophic arthritis.

DISCUSSION OF PAPERS BY HENCH AND BY THOMPSON AND WYATT

DR NATHAN SIDEL, Boston. These papers have been interesting to me because of the report which Dr. Abrams and I made on jaundice in arthritis, mention of which Dr. Hench was kind enough to include in his paper. Since the publication of our report in 1934 I have seen four other patients who showed the analgesic effect of jaundice on their arthritic pain. Two of these patients had obstructive jaundice due to carcinoma of the head of the pancreas, and the articular condition was osteo-arthritis, but there was only slight improvement. The other two patients presented rheumatoid arthritis, and with the onset of catarrhal jaundice the articular pain was markedly alleviated. It would be superfluous for me to state how dramatic the improvement is in such cases, since this has been emphasized by Dr. Hench and Dr. Thompson.

My first experience with bile salt therapy in arthritis was the giving of bile salts by mouth to the first patient in our series after his jaundice cleared. This was in 1933, and whereas the patient previously had to take 8 to 10 tablets of acetylsalicylic acid daily for relief, he felt better with the bile salts and has continued this program ever since. However, this therapy was not successful in the other cases. In 1934 I tried decholin sodium intravenously with ten arthritic patients, but there was no relief. This is consistent with the conclusion drawn from work of Dr. Thompson, that decholin sodium by itself was of no value.

I hope that commercial houses will not exploit bile salts for arthritis in view of the "jaundice analgesia." I look on jaundice as a temporary palliative but not as a cure for arthritis. Is it possible that there is a certain hepatic substance, call it an X substance, that may be helpful when the patient with arthritis takes cinchophen without obtaining toxic effects but that is excreted in excess if jaundice occurs, thus giving marked relief of the arthritis?

WILLIAM B. RAWLS, New York. During the past five years my colleagues and I have been studying the hepatic function of patients with rheumatoid arthritis. Dr. Hench's report that was published in July 1933, in which he pointed out the relief of arthritic pain noted during jaundice, suggested to us that arthritis might be related to hepatic dysfunction. Although one of our patients had had relief from pain during jaundice, we had not considered a possible relation until Dr. Hench's first report appeared.

In another investigation, which included the giving of cinchophen as a clinical test to determine the reliability of cutaneous tests with cinchophen, urticaria developed in nine of the patients. In five of them there was almost complete cessation of pain, lasting for ten days in one case to six months in another. This occurred in cases in which urticaria was severe and lasted for more than five days. As a rule when urticaria was mild, either there was no relief from pain or the relief was only temporary.

Determinations were made of the galactose tolerance, hippuric acid excretion, azorubin S excretion, bilirubin excretion, icterus index, van den Bergh reaction

cholesterol ester content, total cholesterol content and albumin-globulin ratio in most cases, sometimes before and after the administration of cinchophen. When there was relief from arthritic symptoms, the icterus index, the bilirubin content of the blood and the proportion of cholesterol esters to total cholesterol were increased.

Cinchophen toxicity occurred in forty-eight patients, including nine with urticaria. For fifteen of them the icterus index was determined before cinchophen was administered and again after cinchophen toxicity developed. It was increased 3 points in six cases and from 5 to 7 points in four others. If the icterus index remained below 10, there was no relief from symptoms, or the relief was only slight and temporary. If the index was above 10, symptomatic relief was usually more marked and more lasting. Those patients with an icterus index above 10 were considered subicteric. Hench reported one case in his first series and four cases in the present series in which relief was obtained apparently during the subicteric stage. We decided to test the accuracy of icterus index determinations. Repeated readings for a number of specimens indicated a mean technical error of 0.7. The icterus index showed a mean variation of 1.8 from day to day when taken under similar conditions. This indicated that variations of 2 or more points, such as those just mentioned, are significant.

In one case in which mild jaundice developed, lasting for two weeks, there was almost complete cessation of symptoms, but they returned ten days after the disappearance of jaundice. In two other cases of mild jaundice there was complete cessation of symptoms, lasting for about one month. In two instances the arthritic symptoms were worse even though the icterus index was increased to 10 and 12, respectively. Our failure to obtain cessation of symptoms for as long as was obtained by Drs. Hench and Thompson was probably due to the milder degree of jaundice. As Dr. Hench has pointed out, it seems to be a quantitative rather than a qualitative action.

In a number of cases there was a definite decrease in the ratio of cholesterol esters to total cholesterol after cinchophen toxicity developed. In one instance the esters were 64 per cent of the total cholesterol content before the administration of cinchophen and 40 per cent after symptoms of toxicity developed. The icterus index increased from 5.4 to 8.7. There was relief of symptoms for ten days.

In view of the possibility that increased values for serum bilirubin might be a factor in these cases, a number of patients were given intravenous injections of bilirubin, but without appreciable effect on the articular symptoms. Since hearing Dr. Thompson's paper, I am convinced that this was due to insufficient dosage, because our dose never exceeded 3 mg. per kilogram of body weight. This dose gives only a slight increase in the serum bilirubin content after four hours. Our experience with bilirubin has been rather limited, owing to the high cost of the drug. Further study is needed to determine whether an increase in the bilirubin content is responsible for the relief of pain in these cases.

We have also used the sodium salt of dehydrocholic acid (decholin sodium) in a large number of cases. Ten cubic centimeters of 20 per cent solution was given intravenously two or three times each week for four to six weeks or until eight or ten injections had been given. Although improvement seemed to occur in some cases, this drug should be used only for hepatic dysfunction and not as a treatment for arthritis. Its action is probably due to the increased production of bile, which relieves some of the toxicity present.

These observations suggest that the relation between jaundice and the relief of arthritic pain should receive further study.

DR H M MARGOLIS, Pittsburgh The observations of Dr Hench and of Drs Thompson and Wyatt are most interesting, and since they are in line with certain preliminary studies that my colleagues and I have been carrying out in Pittsburgh, I should like to relate briefly our experience

In view of the fact that the occurrence of a significant degree of jaundice, from any cause, frequently inactivates completely an arthritic process for the duration of the icterus, we studied the therapeutic effect of certain components of the icteric state in cases of active rheumatoid arthritis. Because it was most easily available, we studied first the effect of the sodium salt of dehydrocholic acid (decholin sodium), a salt of one of the bile acids, which we injected intravenously daily over a period of a week. We employed this procedure for several patients with rheumatoid arthritis in whom the chief disability was caused by pain, peri-articular swelling, stiffness and soreness. Although in one case the effect during the first few days seemed encouraging, it was soon evident that this improvement was merely coincidental, for the subsequent experience was different and I found no appreciable benefit from the administration of the bile salts. The results were so clearcut that further therapeutic trial of bile salts in arthritis was not attempted.

In view of the possibility that the relation of jaundice to improvement in the arthritic state may depend on some product of hepatic degeneration, we studied the effect of the intravenous and intramuscular injection of autolyzed liver, which was supplied me by Dr W S McElroy, of the University of Pittsburgh. This preparation, which Dr McElroy has employed in the treatment of pernicious anemia, is made by adding a dilute solution of hydrochloric acid to minced beef liver to which small amounts of chloroform are added as a preservative, the mixture being shaken, placed in an incubator and allowed to undergo autolysis for an average of ten days, during which time it is shaken daily. At the end of ten days the undigested material is removed by filtration. Some of this filtrate was used after the reaction to neutrality had been adjusted and after sterilization by Berkefeld filtration. Since this preparation contains various products of protein degradation which are likely to produce severe reactions, the material was diluted in physiologic solution of sodium chloride or 5 per cent solution of dextrose. The intravenous injection of such a solution of autolyzed liver in two cases of atrophic arthritis produced distinct exacerbation of the symptoms of pain, stiffness and soreness. During the course of a series of injections, improvement did not occur, but rather an exacerbation of all the symptoms. The adverse effect was so clearly evident that this procedure also was discarded.

During all this time I felt that the relief of arthritic pain afforded by the icteric state is probably effected not by any single chemical factor but by some combination of factors inherent in the jaundiced state. I am glad to find that the observations of Dr Thompson and Dr Wyatt confirm this view to a large extent. While we did not attempt any study with pure bilirubin or a combination of bilirubin and bile salts, as Dr Thompson did, we played with the idea that the perfect experiment would be the administration to such arthritic patients of whole bile, if some way could be devised to eliminate the known high toxicity of bile. To study the toxicity of whole bile, Dr McElroy and I injected into a dog a preparation of ox bile intravenously. Toxic manifestations resulted immediately, with nausea and vomiting and, later, evidence of cerebral confusion and motor incoordination, from which the dog recovered, however, within twenty-four hours. This reaction was so marked that we did not feel justified in repeating the experiment clinically, particularly since it was evident that such large amounts of whole bile would be required that it would be distinctly hazardous. That is as far as our experiments have gone, but we are still intensely interested in the problem.

of devising some means of duplicating that biologic state which, in spontaneous jaundice, produces these frequently remarkable clinical remissions in the arthritic patient. The present report by Dr. Thompson and Dr. Wyatt points the way to further study along this line—studies which may give some clue to certain biochemical factors capable of influencing the arthritic state favorably.

I can testify to one other point brought out by Dr. Hensch—that the effect of jaundice is somehow selective for rheumatoid arthritis and is apparently ineffective in gout. This was observed in one of my gouty patients recently, in whom an acute exacerbation of gouty arthritis was preceded by acute hepatitis with jaundice. The gouty arthritis in this case appeared, in fact, during the course of the icterus.

DR. PHILIP S. HENSCH, Rochester, Minn. When Dr. Thompson first wrote me last December about his studies, I was greatly interested. Many of the difficulties I have encountered in my study of the phenomenon would be eradicated were one able to produce at will nontoxic jaundice of standard pattern, relatively uniform in type, duration and intensity. In my cases of spontaneous jaundice there were many variables to contend with—the variable duration, extent and intensity of the rheumatism, and the different types, intensity and duration of the jaundice. These differences taught me something about the potency of the reaction and the effectiveness of different types of jaundice but made it difficult to form other than tentative conclusions on certain points. With one group of variables under control, it should be easier to isolate the agent responsible for the phenomenon and the mechanism whereby it works.

It will be noted that I am discussing the procedure of Drs. Thompson and Wyatt not as a therapeutic measure, not as an end in itself, but as a means to an end. Dr. Thompson and I agree on that point. I hope that no one will conclude that jaundice cures rheumatism and that this type of artificial jaundice is the long-sought cure for the disease. To adopt the term therapeutic jaundice at this stage would be forcing a bud to premature flowering. It would court the disappointment of patients and obscure a better goal—a form of treatment simpler, more rational and probably much more effective. By adopting this point of view, however, I am not belittling Dr. Thompson's work in the least. I believe that he has made a most important contribution to the problem, and if his procedure can be readily repeated with equally successful results, he has taken us a long step toward the solution of the problem. First, he has demonstrated a method for successfully producing apparently harmless "jaundice," or hyperbilirubinemia, which should be of value in studying a number of physiologic and clinical problems other than the one under discussion.

Dr. Thompson's study leads to the conclusion that there is some potent reaction between bilirubin and bile salts which is responsible for the phenomenon, and it may be so. As noted in my paper, I have been unwilling to stress the importance of bilirubin for various reasons. Among other phenomena, pregnancy, which seems to have little or nothing to do with bilirubin, often provokes a similarly effective if less dramatic remission in atrophic arthritis. A colleague and I are about to publish details of a study made on about twenty pregnant arthritic women, almost all of whom noted marked amelioration or complete disappearance of symptoms of arthritis when they became pregnant. If this represents a chemical "control," I wonder if nature in the last analysis has more than one way of controlling the arthritic process. There should be some common denominator between the two reactions, and, offhand, bilirubin seems to be excluded. If my four patients who told me their relief came before jaundice was visible were correct, either bilirubin is not responsible, or small amounts are

effective—an idea contradicted by certain data. It is of course possible that the four patients had unrecognized jaundice, but if they did not have or even if they had, subclinical jaundice it suggests that significant excesses of bilirubin are not required.

The study implies also that bile salts are in part responsible for the relief. Certain claims have been made in Europe for bile salt therapy in arthritis. But if a significant increase of bile salts is necessary for the reaction it seems that I should not have seen the phenomenon continue with jaundice in the presence of severe hepatitis when presumably there is a reduction, not an increase in circulating bile salts. The observation that two patients did not obtain relief after four doses of bilirubin but did obtain relief when bile salts was added to the fifth dose of bilirubin is most interesting but needs further investigation. One might argue that a cumulating hyperbilirubinemia was developing that was about to be effective without bile salts. However, Dr. Thompson has made no premature deductions as to what the agent may be. He has merely described a method for use in the elucidation of the problem, and as he has said, much further work is needed to determine how the reaction induces a remission. At least three substances are injected: large amounts of bilirubin, large amounts of sodium carbonate and fairly large amounts of bile salts. The role of each must be fully established.

About two months ago, when his results were consistent enough and the details of his technic were worked out, Dr. Thompson gave me his preliminary plan in order that I might have some experience with it to bring to this discussion. He has described his technic in five sentences, and the method sounds simple enough. But to me it is not as simple as it sounds. Dr. Thompson warned me that we might have difficulties at first and we have had them. First the strong alkali continues to irritate or cause thrombosis in our patients' veins so that the matter of giving eight to twelve consecutive injections to the average thin hyposthenic arthritic patient becomes a problem. According to Dr. Thompson the solution must be made fresh daily (a matter of about two hours) must be administered promptly and must be kept away from sunlight at all times to prevent oxidation of bilirubin. It remains to be proved how necessary some of these precautions are and whether significant oxidation can occur in the ordinary laboratory lighted mainly by electricity and with the solutions in glass containers which are considered essentially impervious to light rays capable of producing much chemical change. Will not heating the solution (unless it is under a layer of nitrogen) produce more oxidation than sunlight or electric light? But these technical difficulties will be solved eventually.

In the eight weeks at my disposal I have been able to treat only six patients, each with active atrophic arthritis. One became jaundiced, and the serum bilirubin content showed several peaks between 15 and 29 mg. But although he received seventeen injections (some of them in doses of 1 Gm.) he noted no relief. One patient received twelve injections and became definitely jaundiced; the serum bilirubin content showed several peaks between 10 and 26 mg. and he noted partial relief only—perhaps 50 per cent for a few days. Unfortunately, venous thrombosis developed and we could not give him more injections. In an attempt to avoid these reactions we buffered the solution bringing it almost to neutrality but two patients treated with such a solution had excretion curves totally different from the others. Neutralization made the solution impotent to produce cumulative hyperbilirubinemia after six injections. Our last two patients have received daily doses of 1 Gm. of bilirubin and 4 Gm. of decholin sodium to produce saturation as fast as possible. They have received eleven and thirteen daily injections respec-

tively, up to the present, both are decidedly jaundiced with the serum bilirubin content showing peaks of 25 and 34 mg and low points of 7.9 and 12.5 mg, yet neither has yet noted any analgesia (After a few more injections both patients experienced considerable relief of pain.) One who had hydrops and fever has noted no change in these features either. Thus, ironically, I am so far unable to corroborate Dr. Thompson's findings, which I should so like to do, since they amply corroborate and extend my own observations on spontaneous jaundice.

Now what is wrong? I do not believe it is Dr. Thompson's fault. I believe he is obtaining the results that he has reported. Realizing that a preliminary experience of only eight weeks gives one little right to draw conclusions, I merely wish to state that there must be differences between his technic and mine which, though they appear to be minor, are of greater importance than we have realized. In going over my technic carefully with him I found two or three little differences which may be important, for example, we added the bile salts before, rather than after, filtration. Nevertheless, one must conclude that the procedure is an empiric, not a rationalized, one. It is not simply a question of dissolving a certain amount of bilirubin in any alkali, adding bile salts and administering the mixture. The hypothetical λ substance may be in or may be engendered by his solution but not by ours, although we have been using the same preparation of bilirubin and bile salts (decholin sodium). Is the λ substance really dependent on his bilirubin-decholin sodium mixture, or is it dependent on something else in his solution? Commercial solutions of bilirubin are not really pure. There are impurities in the bilirubin that both of us have been using. Pure bilirubin contains 8.95 per cent nitrogen, commercial bilirubin contains 7.2 to 8.3 per cent nitrogen. Whether this is a factor and whether oxidation is to be avoided or actually welcomed, these and other details are to be worked out. I am not discouraged by these preliminary differences in results. Indeed, they may help in solving the problem. In the meantime, they emphasize what was said before. Dr. Thompson is not presenting "therapeutic jaundice," but when his method is standardized and rationalized, it may help in realizing to the fullest the therapeutic implications implied in the phenomenon which I have observed occurring with spontaneous jaundice.

DR. HARRY E. THOMPSON, Tucson, Ariz. Dr. Sidel's results with the administration of bile salt alone are similar to ours. Dr. Rawls has used bilirubin alone, but he has given it in doses of only 3 mg. per kilogram, and he has not employed it in conjunction with bile salt.

In regard to Dr. Hench's discussion, when we went over this procedure previous to the meeting it was evident that he had not followed the exact procedure which I gave him a few months ago. He had made several changes. Both he and I agree that although these are minor changes, they are perhaps of major importance. This, I am sure, accounts for differences in our results. In an effort to confirm our work he has mentioned that one patient was 50 per cent improved. This indicates to me that despite the changes made in the procedure, he was sufficiently close at that time to approximate our results in part. I think that closer adherence to the procedure—both as to the preparation and as to the administration—will result in comparable clinical results. That nontoxic jaundice can be produced is apparent, as Dr. Hench has confirmed our work with relation to its production. Dr. Hench is to be congratulated for his keen observation that jaundice intervening clinically may produce a remission in atrophic arthritis.

I, too, am of the opinion that both bilirubin and bile salt should be kept free from exploration. To exploit such substances, promising as they appear, is undesirable and unwarranted at this time.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S. McCANN, M.D.

ROCHESTER, N. Y.

The period covered by this review is marked chiefly by notable achievements in the study of renal function and of the pathogenesis of renal hypertension. These achievements consist in the bringing to fruition of investigations which have covered a considerable time. These investigations have been chiefly in the field of physiology and of experimental pathology. The fruit of the achievements consists in providing the clinical investigator with sound tools with which to proceed. Many other valuable investigations have been reported, the ultimate significance of which is not so apparent. Attention will first be given to those fields in which the pattern of the mosaic may be most clearly discerned.

STUDIES OF RENAL FUNCTION

The modern theory of renal function, based on the conception of glomerular filtration and tubular resorption, appears each year to be more firmly established. For a long time it has been apparent that there is need of quantitative methods for the separate measurement of these two phases of the secretion of urine. Progress along this line began with the measurement of the urea clearance by Van Slyke and his co-workers. The conception of the "clearance" was applied to other substances which are either normally present in the plasma or which may be made to appear in it. The proposal of Rehberg and Holten that creatinine clearance could be used as a measure of glomerular filtration has been a fruitful one, in that it has been subjected to critical investigation in the course of which comparisons have been made with other substances, such as sucrose, phenolsulfonphthalein (phenol red), inulin and several other substances. A good review of the extensive investigations along these lines is to be found in the recent monograph by Homer Smith¹ entitled "The Physiology of the Kidney."

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¹ Smith, Homer W. The Physiology of the Kidney, New York, Oxford University Press, 1937.

In order to secure a perfect measure of glomerular filtration it is necessary to measure the clearance of some substance which is not reabsorbed in the tubules. Richards, Westfall and Bott² have completed conclusive experiments on the use of creatinine and inulin for this purpose. In previous experiments of Hendrix, Westfall and Richards, inulin, which has a molecular weight of about 5,000, was found in the glomerular filtrate of Necturi in the same concentration as in the plasma. Richards takes the inulin clearance as the equivalent of glomerular filtration. Over a wide range of urinary flow and of concentrations of plasma and urine the kidneys of normal dogs were found to excrete both inulin and creatinine by glomerular filtration. Neither substance was found to be reabsorbed from the tubules either actively or by diffusion. These authors, however, studied a dog which had previously been poisoned with uranium. In this case insulin was discovered to be excreted consistently at a faster rate than was creatinine. This was taken to indicate that the normal impermeability of the tubules to back diffusion of creatinine had been impaired so that 13 per cent was returned to the blood. From these observations it appears that inulin provides a better measure of glomerular filtration than creatinine under some conditions of tubular injury. Other types of tubular injury will need to be studied before one can be certain that similar back diffusion of inulin may not occur.

Goldring and Smith³ have investigated the phenolsulfonphthalein clearance at low plasma levels as a measure of tubular activity, since at these low levels most of the dye is bound by the plasma colloids. In their observations glomerular filtration was measured by the inulin clearance. They have attempted to draw conclusions as to the states of function in glomeruli and tubules by changes observed in the phenol-sulfonphthalein inulin clearance ratios. They indicate, however, that changes may occur as a result of changes in renal blood flow.

It appears to me, however, that another phase of phenolsulfonphthalein clearance must be considered, as a result of some investigations of Ehrstrom⁴ concerning the disappearance of congo red from the plasma in amyloid disease. Ehrstrom found that in certain conditions the binding power of the plasma proteins for congo red is impaired. If this is true there might also be conditions in which plasma proteins would bind phenolsulfonphthalein less securely. This would alter the

2 Richards, A. N., Westfall, B. B., and Bott, P. A. Inulin and Creatinine Clearances in Dogs, with Notes on Some Late Effects of Uranium Poisoning, *J. Biol. Chem.* **116** 749, 1936.

3 Goldring, W., and Smith, H. W. Differentiation of Glomerular and Tubular Function in Glomerulo-Nephritis, *Proc. Soc. Exper. Biol. & Med.* **37** 180, 1937.

4 Ehrstrom, M. C. Ueber veränderte physikalische Eigenschaften der Plasma-proteine bei Nephrose, *Acta med. Scandinav.* **90** 427, 1936.

normal relations between free and bound phenolsulfonphthalein, on which the assumptions of Goldring and Smith were based

Winkler and Parra⁵ compared the clearances of creatinine, sucrose and urea of normal and nephritic subjects. The order of magnitude of the clearances is creatinine > sucrose > urea. They vary together. For normal subjects the creatinine clearance was found to be higher immediately after ingestion of creatinine, with a tendency to decrease with time. By subjects with renal disease for whom these clearances were reduced, the same relative magnitudes were retained, and a tendency of the creatinine clearance to fall off with time was not observed.

In Copenhagen, studies of the renal function during the course of scarlet fever and scarlatinal nephritis have been made by Gram⁶. Daily measurements were made of the urea clearance and urinary sediment. For 7 patients with scarlet fever and complications other than nephritis, high clearance values were found during the first ten days. Later, during the fourth and fifth weeks, low values were usually observed. All patients excreted casts and erythrocytes at various times. In 5 the blood pressure was normal, in 2 it was elevated. The patients with scarlet fever in whom nephritis developed showed a decrease in urea clearance by the end of the first week, in contrast to those in whom nephritis did not develop and for whom low clearance values were obtained mostly in the fourth week.

In other acute infections, high rates of urea clearance have been observed at the height of the disease. In 1931 Goldring⁷ observed high values in the acute stage of rheumatic fever, while low values were observed during convalescence. He⁸ made similar observations in cases of lobar pneumonia. Similarly, Farr and Abernethy⁹ obtained high values for young persons with lobar pneumonia, not only during the precritical stage but for a month afterward. These high rates of urea clearance were chiefly observed for persons under 40 years of age. For older subjects less elevation was found.

5 Winkler, A. W., and Parra, J. The Measurement of Glomerular Filtration Creatinine, Sucrose and Urea Clearances in Subjects Without Renal Disease, *J. Clin. Investigation* **16** 859, 1937, The Measurement of Glomerular Filtration Creatinine Sucrose and Urea Clearances in Subjects with Renal Disease, *ibid* **16** 869, 1937.

6 Gram, C. N. J. Renal Function During the Course of Scarletine and Scarlatinal Nephritis, *Acta med. Scandinav. (supp.)* **78** 778, 1936.

7 Goldring, W. Studies of the Kidney in Acute Infection. II. Observations of the Urea Clearance Test in Acute Rheumatic Infection, *J. Clin. Investigation* **10** 345, 1931.

8 Goldring, W. Kidney in Acute Infection. Sediment Count (Addis) in Lobar Pneumonia, *J. Clin. Investigation* **10** 355, 1931.

9 Farr, L. E., and Abernethy, T. J. Renal Physiology in Lobar Pneumonia, *J. Clin. Investigation* **16** 421, 1937.

ADDIS SEDIMENT COUNTS IN ACUTE INFECTIONS

In pneumonia Farr and Abernethy⁹ found no abnormal values for erythrocytes. The number of casts was usually increased, that of the hyaline casts especially. Granular casts were found in the cases of more severe pneumonia. Proteinuria was generally slight, rarely over 0.1 Gm. of protein being excreted daily. Abnormalities of the urinary sediment tended to disappear as the fluid balance was reestablished. No instance of nephritis was observed in their series of 28 patients. In 1931 Goldring⁸ observed 2 patients who had diffuse glomerulonephritis during convalescence from pneumonia, but in general his findings agreed with those of Farr and Abernethy.

Gram⁶ believes that the majority of patients with scarlet fever have latent nephritis and that they may be grouped as follows: (1) those with intermittent hematuria but normal blood pressure and urea clearance, (2) those with constant and profuse cylindruria, with either a normal or an elevated blood pressure, (3) those with chemically demonstrable hematuria, increased blood pressure and slight edema but no azotemia.

This recalls the work of Lyttle,¹⁰ who studied 14 patients with scarlet fever, finding that all showed transient increase in the excretion of protein and formed elements in the period from eight to forty-five days after the onset. He said he believed that renal damage was so slight that only unusually careful examination would reveal it and that in the majority of cases the nephritis was aborted by a satisfactory immunologic adjustment.

In a previous review,¹¹ reference was made to the work of Goldring and Wykoff, who found that the excretion of formed elements and protein occurred in excess of normal in 16 cases of rheumatic fever.

Concerning the prognosis for recovery of children who have had postinfectious nephritis, there is some divergence of views. Boyle, Aldrich, Frank and Borowsky¹² followed the urinary sediment counts of 25 children for periods of one-half to eight years. With the exception of 1 girl, all showed normal counts. In this 1 case, in which occult hematuria was present, hydronephrosis was discovered.

On the other hand, Snoke¹³ presents the results of a study of 154 children observed between 1920 and 1936 in the Stanford Children's

10 Lyttle, J. D. The Addis Sediment Count in Scarlet Fever, *J. Clin. Investigation* **12** 95, 1933.

11 McCann, W. S. Bright's Disease. A Review of Recent Literature, *Arch. Int. Med.* **55** 512 (March) 1935.

12 Boyle, H. A., Aldrich, C. A., Frank, A., and Borowsky, S. The Addis Count in Children Following Clinical Recovery from Post-Infectious Nephritis, *J. A. M. A.* **108** 1496 (May 1) 1937.

13 Snoke, A. W. Stages, Prognosis and Duration of Glomerular Nephritis in Childhood, *Am. J. Dis. Child.* **53** 673 (March) 1937.

Clinic who had glomerulonephritis. Of these, 37 per cent are now healed, 21 per cent are dead and 42 per cent still have active nephritis. Snoke feels that in practically no case can glomerulonephritis of more than two years' duration be expected to heal. He estimates the eventual mortality rate in this series of cases at 40 per cent. The persistence of latent glomerulonephritis is frequently missed unless quantitative examination of properly concentrated urine is made.

In the accompanying table are recorded the sediment counts observed by Boyle and his co-workers¹² for patients who had recovered from glomerulonephritis, compared with the various normal standards of Addis,¹⁴ Lyttle,¹⁵ Goldring¹⁶ and Naeraa.¹⁷

*Sediment Counts for Children Who Had Recovered from Nephritis Compared with Normal Standards of Various Authors **

	Status of Child	Number of Casts	Number of Erythrocytes	Number of Leukocytes and Epithelial Cells
Boyle ¹²	After recovery from nephritis	0 18,611	0 114,000	0 990,000
		3,401	19,817	337,000
Addis	Normal	0 4,270	0 425,500	32,400 1,835,000
		1,040	65,750	322,500
Lyttle	Normal	0 12,916	0 129,900	9,000 2,822,000
		1,035 \pm 123	15,181 \pm 1,400	322,184 \pm 25,500
Goldring	Normal	0 9,200	0 1,530,000	24,000 2,430,000
		1,300	146,000	540,000

* The upper figures represent the range of variation, and the lower figure represents the mean value.

PREVENTION OF GLOMERULONEPHRITIS

Peters and Cullum¹⁸ have compared the statistics on the incidence of scarlet fever and of scarlatinal nephritis in the Ham Green Hospital in Bristol, England, for the period from 1910 to 1936. The incidences varied, but in the period from 1930 to 1934 an especially low incidence of nephritis was noted. During this period Peters was administering thyroid and iodine to the patients during the first fortnight of the

¹⁴ Addis, T. Clinical Classification of Bright's Disease, J. A. M. A. **85** 163 (July 18) 1925.

¹⁵ Lyttle, J. D. Addis Count in Normal Children, J. Clin. Investigation **12** 87, 1933.

¹⁶ Goldring, W. Clinical Application of Sediment Count (Addis), Am. J. M. Sc. **182** 105, 1931.

¹⁷ Naeraa, A. Om Addis' urinsediment bestemmels, Hospitalstid **77** 1444, 1934.

¹⁸ Peters, B. A., and Cullum, I. M. A Study in Prevention Brit. M. J. **1** 1020 (May 15) 1937.

disease. The difference in incidence was 2.3 times the standard deviation and seemed significant. However, during the following year scarlet fever was very severe, and the incidence of nephritis increased in spite of this method of treatment. Therefore, alternate patients were used as controls for a comparison of the effects of the thyroid and iodine treatment and for the evaluation of Osman's alkalization treatment in the prevention of nephritis after scarlet fever. For Osman's method there were 124 test cases and 134 controls, with no significant differences in the incidence of albuminuria and nephritis. For the thyroid and iodine treatment there were 165 test cases and 162 controls, with no significant differences between them. It appears, therefore, that the evaluation of preventive measures in such a variable disease is better accomplished by studying alternate cases than by observation of year to year variations. It is apparent also that means of prevention of postscarlatinal nephritis, apart from the prevention of scarlet fever, are still to be found.

EXPERIMENTAL NEPHROTOXIC NEPHRITIS

In a previous review¹⁹ mention was made of the production of nephritis by Masugi and by Smadel, who used a nephrotoxic serum. Smadel and Farr²⁰ report the clinical and functional studies of the experimental nephritis thus produced. Clinically it is characterized by albuminuria, cylindruria and anasarca but not by hematuria. The rapidity of its development varies with the dose of nephrotoxin, ranging from two weeks to eleven months. The milder forms progress to renal insufficiency by stages resembling those of diffuse glomerulonephritis in man. Several methods are described for determination of the urea clearance of rats, together with the method of Moberg for measurement of the blood pressure of these small animals.

Smadel²¹ describes the lesions in the kidneys of rats with nephritis. They are characterized by the early swelling of the intercapillary substance of the glomerular tuft. Thrombi were present only in those cases in which anaphylactoid reactions occurred, and these were due to other factors than pure nephrotoxin. Tubular degeneration was noted, followed later by scarring of glomeruli and tubules and by widespread vascular disease, with secondary changes in the heart and brain and elsewhere.

19 McCann, W. S. Bright's Disease. A Review of Recent Literature, *Arch Int Med* **60** 167 (July) 1937.

20 Smadel, J. E., and Farr, Lee E. Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum. II. Clinical and Functional Studies, *J Exper Med* **65** 527, 1937.

21 Smadel, J. E. Pathological Studies of the Acute and Chronic Disease, *J Exper Med* **65** 541, 1937.

Swift and Smadel²² report that they were able to prevent the injurious effects of the administration of nephrotoxic serum by giving a saline extract of rat kidney intravenously to rats before injection of the nephrotoxic serum. The nephrotoxic effect was not inhibited by the administration of a similar extract of rat liver, although this extract was capable of absorbing the nephrotoxin *in vitro*.

Farr and Smadel²³ have studied the effects of diet on the course of nephrotoxic nephritis in rats which received a single injection of nephrotoxin. These were divided into three groups and were given three types of diets which were isocaloric, as follows: (1) 5 per cent protein, 64 per cent carbohydrate and 27 per cent fat, (2) 18 per cent protein, 51 per cent carbohydrate and 27 per cent fat, (3) 40 per cent protein, 29 per cent carbohydrate and 27 per cent fat. For all three the same salt mixture and sources of vitamins were used.

In group 1, 13 of the 15 rats survived, and the evidences of nephritis had disappeared in eight and one-half months. At this point 5 of the rats were given diet 3, and in the ensuing months 3 of them showed albumin and casts in the urine, though they had normal renal function.

In every animal on diet 3 progressive nephritis developed, and all but 2 were dead of renal failure in six months.

On diet 2, 8 of the 15 were dead of renal failure in five and one-half months. Of the remainder, 6 were definitely abnormal and 1 recovered.

It is apparent from these studies that the course of experimental nephritis is markedly and adversely influenced by a high proportion of protein in the diet. It appears to me that these results should be examined in the light of what constitutes a normal diet for the rat and for man. It must not be too readily assumed that because excessive proportions of protein are harmful, normal proportions will also prove to be so. The normal diet of man, given wide and free choice, will be found to derive about 15 per cent of its calories from protein. Normal Eskimos tolerate proportions as high as 45 per cent. It may well be that excessively high proportions will be found to have an adverse effect on the course of nephritis in man. This should not be taken as an excuse for protein starvation, since clinical studies by Keutmann and McCann²⁴ of human beings have revealed no adverse effects from a ration of protein sufficient to permit deposition of protein to replace

22 Swift, H. F. and Smadel, J. E. Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum. IV. Prevention of the Injurious Effects of Nephrotoxin *in Vivo* by Kidney Extract, *J. Exper. Med.* **65** 557, 1937.

23 Farr, L. E., and Smadel, J. E. Influence of Diet on the Course of Nephrotoxic Nephritis in Rats, *Proc. Soc. Exper. Biol. & Med.* **36** 472, 1937.

24 Keutmann, E. H., and McCann, W. S. Dietary Protein in Hemorrhagic Bright's Disease, *J. Clin. Investigation* **9** 973, 1932.

large losses through albuminuria Keutmann and Bassett²⁵ present data which show that maximal synthesis of new protein may be achieved with diets which are well within the limits of a normal intake of protein and which could by no means be considered high in protein

Bearing on this same question is a paper by Blatherwick and Medlar,²⁶ who produced chronic nephritis in rats by feeding diets high in protein, some containing as much as 72 to 75 per cent liver or casein. Some of their diets which consisted of 25 per cent milk protein and 12 per cent beef protein led to renal injury, but diets in which the protein was as low as 20 per cent apparently did not produce these results

HYPERTENSION IN NEPHROTOXIC NEPHRITIS

Arnott, Kellar and Mathew²⁷ produced nephritis by the method of Masugi. If one kidney was denervated prior to induction of nephritis, the anatomic changes produced were identical in the two kidneys. Hypertension was observed in the animals with experimental nephritis. It was found that the development of hypertension could be prevented by denervation of the kidneys before induction of nephritis. If denervation was carried out afterward, the hypertension was terminated. These results are similar to those reported by these authors previously concerning the hypertension of oxalate nephritis.

HYPERTENSION PRODUCED BY RENAL ISCHEMIA

Goldblatt²⁸ has recently reviewed his own work on the production of hypertension in dogs by means of renal ischemia induced by means of metal clamps applied to the renal arteries, together with the accumulating evidence of the formation of a humoral pressor substance in the ischemic kidneys. This substance is believed to act independently of the nervous mechanism of the kidney, and in Goldblatt's opinion it is independent of the endocrine glands, with the possible exception of the adrenal cortex. He gives a tabular review of the various procedures of other investigators by means of which transient hypertension has been produced by renal injury.

25 Keutmann, E. H., and Bassett, S. H. Dietary Protein in Hemorrhagic Bright's Disease. II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Protein, *J. Clin. Investigation* **14** 853, 1935.

26 Blatherwick, N. R., and Medlar, E. M. Chronic Nephritis in Rats Fed High Protein Diets, *Arch. Int. Med.* **59** 572 (April) 1937.

27 Arnott, W. M., Kellar, R. J., and Mathew, G. D. Hypertension Associated with Experimental Serum Nephritis, *Edinburgh M. J.* **44** 205, 1937.

28 Goldblatt, H. Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* **11** 69, 1937.

Goldblatt, Gross and Hanzal²⁹ have found that excision of the lower four dorsal sympathetic ganglions and the thoracic portion of the splanchnic nerves on both sides does not prevent, cure or permanently lower the hypertension produced by renal ischemia

Goldblatt³⁰ reports success in his efforts to produce hypertension in giant macaques by the same means (clamps on renal arteries) previously used on dogs. Transient hypertension is produced by unilateral application of a clamp, a persistent elevation of both systolic and diastolic pressures follows the bilateral application

Child and Glenn³¹ accomplished denervation of a dog's kidney by transplanting it completely to the pelvis and giving it a blood supply from the femoral vessels. Application of the clamp, with the production of ischemia, caused transient hypertension. Alpert, Alving and Grimson³² performed total sympathectomy on a dog with sustained hypertension produced by a Goldblatt clamp. The blood pressure fell but remained above the control level. When the clamps were applied to a dog which had previously been subjected to total sympathectomy, hypertension was produced

Wood and Cash³³ report the production of persistent hypertension in dogs by means of Goldblatt's clamps

Harrison, Blalock, Mason and Williams³⁴ have obtained pressor effects from saline extracts of dog kidneys when these extracts were given to rats anesthetized with pentobarbital sodium. Extracts from normal dog kidney produced a significant rise in blood pressure, but extracts from kidneys rendered ischemic produced a greater rise. When one kidney only was rendered ischemic, its extract gave a greater pressor response than did the normal kidney from the other side

29 Goldblatt, H. Gross, J., and Hanzal, R. F. Studies on Experimental Hypertension. II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, *J. Exper. Med.* **65** 233, 1937

30 Goldblatt, H. Studies in Experimental Hypertension. III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, *J. Exper. Med.* **65** 671, 1937

31 Child, C. C., and Glenn, F. Experimental Hypertension in Dogs by Constricting the Artery of a Single Transplanted Kidney, *Proc. Soc. Exper. Biol. & Med.* **37** 217, 1937

32 Alpert, L. K., Alving, A. S., and Grimson, K. S. Effect of Total Sympathectomy on Experimental Renal Hypertension in Dogs, *Proc. Soc. Exper. Biol. & Med.* **37** 1, 1937

33 Wood, J. E., Jr., and Cash, J. R. Experimental Hypertension. Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, *J. Clin. Investigation* **15** 543, 1936

34 Harrison, T. R., Blalock, A., Mason, M. F., and Williams, J. R., Jr. Relation of Kidneys to Blood Pressure. Effects of Extracts of Kidneys of Normal Dogs and of Dogs with Renal Hypertension on Blood Pressure of Rats, *Arch. Int. Med.* **60** 1058 (Dec.) 1937

From the foregoing review it is clear that Goldblatt's findings have received ample confirmation by several workers. It seems to be well established that the hypertension produced by renal ischemia is of humoral origin and independent of the renal innervation. The pressor substance appears to arise within the ischemic kidney.

HYPERTENSION IN RELATION TO PYELONEPHRITIS

Longcope³⁵ describes chronic pyelonephritis of adults of hematogenous origin, usually with insidious beginnings but occasionally having as an onset acute pyonephritis. Infection with *Bacillus coli* is usually responsible. The slow, insidious progress over a period of years may lead ultimately to renal insufficiency, frequently but not always associated with intermittent or persistent hypertension. Hemorrhagic retinitis may occur, but arteriosclerosis is not a conspicuous feature, in fact, arteriolar sclerosis was minimal in his cases post mortem.

The recognition of the disease during life is facilitated by urinary cultures and by intravenous pyelograms, which reveal dilatation of the ureters in the absence of obstruction and peculiar deformities of the pelves and calices. In 3 of 9 fatal cases the disorder was associated with diffuse glomerulonephritis.

A good description of the pathologic anatomy of pyelonephritic contracted kidneys is given by Staemmler and Dopheide.³⁶ These writers describe the widening of the ureters and the distortions and irregularities of the pelves without obvious obstruction, the very irregular contraction and scarring of the renal parenchyma which is more marked than that to be expected in hydronephrotic kidneys and the very moderate changes in the mucosa of the pelves, ureters and bladder. Microscopically these kidneys show a chronic inflammatory process with slowly progressing obliteration of the cortex, which completely disappears in some places and assumes a thyroid-like appearance in others. Glomeruli show adhesions, in some places there is hyalinization, and in other places there is replacement by a granulation-like tissue.

These cases recall the report of Wilson and Schloss³⁷ who described the pathologic changes in the kidneys of infants with pyuria. The kidneys were the seat of an interstitial suppurative process with foci which ranged all the way from simple clusters of mononuclear and polymorphonuclear cells near blood vessels to frank abscesses. Changes

35 Longcope, Warfield T. Chronic Bilateral Pyelonephritis Its Origin and Its Association with Hypertension, *Ann Int Med* **11** 149, 1937.

36 Staemmler, M., and Dopheide, W. Die pyelonephritische Schrumpfniere, *Virchows Arch f path Anat* **277** 713, 1930.

37 Wilson, J. R., and Schloss, O. M. Pathology of So-Called "Acute Pyelitis" in Infants, *Am J Dis Child* **38** 227 (Aug) 1929.

in the pelves, ureters and bladder differed from those occurring with obstruction of the urinary tract, which have been well described recently by Helmholtz ³⁸

Butler ³⁹ has recently reported 15 cases of chronic pyelonephritis in children which was associated with hypertension over a period of years before there was appreciable diminution of renal function. Six of these patients died and 9 are living. Two cases of unilateral pyelonephritis with hypertension are reported in which removal of the infected kidney relieved the hypertension. Butler points out the difficulty in many cases of trying to decide whether one is dealing with primary vascular hypertension or secondary renal hypertension. In some cases of pyelonephritic contracted kidney the arteriolar sclerosis may be like that of nephrosclerosis, and the relative effects of infection and vascular change may be difficult to evaluate. It is also to be recalled that patients with malignant hypertension frequently give a history of antecedent renal infection.

RENAL LESIONS IN TOXEMIA OF PREGNANCY

The close relation between the foregoing discussion and toxemia of pregnancy is emphasized by Zimmerman and Peters ⁴⁰ in a review of 23 cases of death due to "toxemias of pregnancy." Characteristic tubular and glomerular lesions were usually present in those dying in an acute eclamptic state, but they were not noted exclusively in eclampsia. Lesions characteristic of malignant nephrosclerosis were frequently seen. It appears that a variety of infectious and vascular renal diseases may act as the predisposing cause of toxemia of pregnancy. As Zimmerman and Peters express it, "Pregnancy gives them a distinctive coloration and an explosive character."

NEPHROSES

Talbott, Coombs and Consolazio ⁴¹ describe the electrolyte balance during recovery from mercurial nephrosis, beginning on the seventh day and extending through five months, of a patient who had been anuric for six days. They observed (1) depletion of the base and

38 Helmholtz H F. Infection of the Renal Parenchyma from the Pelvis of the Kidney, *Am J Dis Child* **54** 1 (July) 1937

39 Butler, A M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889, 1937

40 Zimmerman, H M, and Peters, J P. Pathology of the Pregnancy Toxemias, *J Clin Investigation* **16** 397, 1937

41 Talbott, J H, Coombs, F S, and Consolazio, W V. Electrolyte Balance During Recovery from Mercury Bichloride Poisoning, *Arch Int Med* **60** 301 (Aug) 1937

chloride of the body, (2) increase in the content of undetermined acid, (3) retention of phosphates and nitrogenous products and (4) loss of serum protein and hemoglobin

Kerkhof⁴² discusses colloid osmotic pressure as a factor in the formation and absorption of edema fluid. Using the method of Schade he found the normal colloidal osmotic pressure to be 21.4 ± 2.5 mm of mercury in man and 18.5 mm in dogs. In nephrosis and nephritis the colloid osmotic pressure is usually lower than 15 and often as low as 8 mm. At 16 mm, edema fluid either is not present or is in process of absorption. He uses solution of acacia to obtain diuresis by raising the colloid osmotic pressure. In spite of previous reports of disastrous results of giving solution of acacia, Lepore⁴³ recommends it. He believes that the deleterious effects can be avoided and that in selected cases it is of value. He finds doses of 30 Gm of acacia effective and employs it in 6 per cent solution.

McMaster⁴⁴ has made a comparative study of the lymphatic vessels and the flow of lymph in the skin of subjects with cardiac or with renal edema (the latter without hypertension or heart failure). He employed intradermal injections of small amounts of a vital dye "patent blue V," and studied the effects of posture, activity and venous obstruction on lymph flow.

In both cardiac and nephrotic edema the lymphatic vessels were patent. In cardiac edema there was stagnation of the lymph, in contrast to the nephrotic edema, in which the flow of lymph was greater than normal, even during periods of fluid equilibrium, and extraordinarily rapid during periods of diuresis.

McMaster believes that the lymphatic vessels are so dilated in cardiac edema that the valves are incompetent. He seems to have overlooked the significance of the high venous pressure in heart failure which tends to impede the return of lymph to the venous system.

Ehrstrom⁴ reports an investigation which has an important bearing on the use of the congo red test in the nephroses, in which the dye disappears rapidly from the blood stream, particularly in amyloid disease. This disappearance of dye cannot be accounted for entirely by its appearance in the urine. When he tested the plasma of normal men by adding congo red in vitro, he found that the dye was so bound by

42 Kerkhof, A. C. Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, *Ann Int Med* **11** 867, 1937.

43 Lepore, M. J. Acacia Therapy in Nephrotic Edema, *Ann Int Med* **11** 285, 1937.

44 McMaster, P. D. The Lymphatics and Lymph Flow in the Edematous Skin of Cardiac and Renal Disease, *J Exper Med* **65** 373, 1937, Changes in the Cutaneous Lymphatics of Human Beings and in Lymph Flow Under Normal and Pathological Conditions, *ibid* **65** 347, 1937.

the proteins that little of it could be removed by shaking with animal charcoal. When the same test was applied to plasma from patients showing massive albuminuria, it was found that the dye was loosely bound so that a large part of it could be removed by charcoal. These investigations show that this alteration in the plasma is not characteristic of amyloid disease alone but occurs in other nephropathologic conditions in which massive albuminuria and tubular degeneration occur, even in a case of severe chronic passive congestion of the kidneys. This phenomenon is looked on as primarily due to changes in the plasma proteins themselves.

Another investigation which has similar implications as to alteration of the plasma proteins is that of Kendall⁴⁵. He finds that the familial globulin, which is insoluble in water but soluble in dilute salt solution, is composed of two water-soluble fractions, alpha globulin and globulin x which may be separated by a specific precipitin. Kendall finds that normal serum globulin is about 55 per cent alpha globulin and that normal serum contains 1.1 to 2.1 Gm. of alpha globulin and 0.4 to 1 Gm. of globulin x. Patients with alcoholic cirrhosis of the liver and others with chronic nephritis show alterations in the quantities and proportions of these two fractions.

Briggs⁴⁶ reports an interesting study of the formation of ammonia by the kidneys in nephrosis. By correlating data on the ratio of ammonia to excess excretion of acid and the rate of flow of urine, he finds in nephrosis evidence that the tubules tend to respond to the stimulus of acid in them by an unusually high secretion of ammonia. He believes that in nephrosis the low volume of urine, which is found in spite of normal glomerular filtration, is due to excessive resorption of threshold substances, and he believes that this may be a contributory factor in the production of nephrotic edema.

A study has been made by Keutmann and Bassett⁴⁷ of the factors which influence proteinuria. They observed simultaneous increase in the protein content of the urine and the urea clearance when the protein of the diet was increased, when diuretics were administered or when the volume of the blood plasma was increased by transfusion of plasma. They conclude that the protein content of the urine varies with

45 Kendall, F. E. Studies on Serum Proteins. I. Identification of a Single Serum Globulin by Immunological Means, Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, *J. Clin. Investigation* **16** 921, 1937.

46 Briggs, A. P. Functional Activity of Renal Epithelium in Certain Types of Nephritis as Indicated by Secretion of Ammonia, *Arch. Int. Med.* **60** 193 (Aug.) 1937.

47 Keutmann, E. H., and Bassett, S. H. Studies on the Mechanism of Proteinuria, *J. Clin. Investigation* **16** 767, 1937.

glomerular permeability, with the rate of glomerular filtration, with the amount of new material present in the diet or in reserves of the body from which plasma proteins may be derived, and with artificial increase of the plasma protein content, such as follows transfusion

"HEPATORENAL SYNDROME"

The term hepatorenal syndrome appears frequently in the literature. In the minds of some it connotes serous inflammatory edema of the kidney, occurring in some cases of severe hepatic injury terminating in anuria and uremia. Nonnenbruch⁴⁸ finds that this lesion of the kidney is not invariably present. The disturbance of renal function may be of extra-renal origin. This syndrome may occur in a wide variety of states, ranging from Weil's disease to food poisoning.

Elsom⁴⁹ studied 16 patients with obstructive jaundice and 1 with arsenical hepatitis, who gave evidence of renal injury. The urine contained an excessive number of casts, epithelial cells and leukocytes. Hematuria and albuminuria were inconspicuous. The urea clearance was frequently reduced. As the jaundice subsided, evidences of renal injury disappeared.

HYPERPARATHYROIDISM IN RENAL DISEASE

Highman and Hamilton⁵⁰ have shown that there is an increased activity of the parathyroid glands in chronic renal disease, as measured by the method of Hamilton and Schwartz. This method consists of injecting the blood to be tested into rabbits and observing the degree of increase in the calcium content of the serum which ensues if parathyroid hormone is present.

After daily injection of phosphate into rabbits, hyperplasia of the parathyroid glands was observed by Drake, Albright and Castleman⁵¹. These experiments elucidate the method by means of which such hyperplasia may arise in chronic renal insufficiency with phosphate retention.

MISCELLANEOUS REPORTS

Bliss⁵² offers an interesting explanation of the ulcerative stomatitis sometimes seen in uremic patients. He found urease present in the

48 Nonnenbruch, W. Ueber das entzündliche Odem der Niere und das hepatorenale Syndrome, *Deutsche med. Wchnschr.* **63** 7 (Jan.) 1937.

49 Elsom, K. A. Renal Function in Obstructive Jaundice, *Arch. Int. Med.* **60** 1028 (Dec.) 1937.

50 Highman, W. J., Jr., and Hamilton, B. Hyperparathyroidism in Kidney Disease, *J. Clin. Investigation* **16** 103, 1937.

51 Drake, T. G., Albright, F., and Castleman, B. Parathyroid Hyperplasia in Rabbits Produced by Parenteral Phosphate Administration. *J. Clin. Investigation* **16** 203, 1937.

52 Bliss, S. Cause of Sore Mouth in Nephritis, *J. Biol. Chem.* **121** 425 1937.

tartar of the teeth When the urea content of the saliva is increased the liberation of ammonia is believed to cause the injury to the cheeks and gums adjacent to the deposits of tartar To relieve the condition, tartar should be removed

Gamble⁵³ has written a masterly study of the renal defense of extracellular fluid He studied the water economy resulting from the fact that mixtures of urea and salt can be removed in the urine in higher concentrations than can be reached by water or salt alone In view of the fact that sluggish production of ammonia in chronic nephritis results in a deficit of fixed base, an adequate intake of salt is required to prevent gradual dehydration

53 Gamble, James L Renal Defense of Extracellular Fluid Control of Acid Base Excretion and the Factors of Water Expenditure, Bull Johns Hopkins Hosp **61** 174, 1937

Book Reviews

Food and the Principles of Dietetics By Robert Hutchison, M D, and V H Mottram, M A Eighth edition Price \$6.75 Pp 634, with 32 figures and 3 colored plates Baltimore William Wood & Company, 1936

This book has a proud and honorable record Forty years ago Dr Hutchison began giving the students of the London Hospital a course of lectures on dietetics, and so gratifying was the reception accorded these lectures that out of them grew the present volumes The first edition appeared on this side of the water in 1901 Ever since, from time to time, reprintings and new editions have been forthcoming as often as seemed necessary Each new edition has been much like its predecessor The ultimate goal always has been to make the subject of dietetics interesting, alive and up-to-date, hence, each edition has been written so that it is readable, and whatever minor changes were necessary have been made in the text so as to keep the subject matter abreast of the times The eighth edition is no exception

The *Lancet*, in 1900, set its stamp of approval on the first edition by saying that it was to be cordially recommended as dealing most instructively with a subject which is not generally studied with the care which its importance demands 'Nowadays we are presented with all manner and kinds of foodstuffs, some undoubtedly of value but others undoubtedly worthless, and it is important that all those who are concerned with the subject of dietetics (and who are not) should have some reliable information upon which to found an opinion'

In the United States there has seemed to be slowness in appreciating the soundness and reliability of the information contained in this book The ARCHIVES of INTERNAL MEDICINE, for instance, has never before reviewed it, and *The Journal of the American Medical Association* has acknowledged only the third, fifth and seventh editions Of the latter, however, it was said (*J A M A* **101** 953 [Sept 16] 1933), "It is a valuable textbook for students and practitioners of medicine and those desiring a general basic knowledge of foods and nutrition All classes of common foods and the important problems of nutrition are given appropriate attention References to important original papers are given in footnotes, the subject matter is simply and clearly presented" What was stated then applies with equal fairness now

At this late date the ARCHIVES feels presumptuous in attempting to compliment a book so much older and more mature than itself However, a curtesy is dropped to the eighth edition with much pleasure, this edition, like all the others, is a sane, practical and stimulating textbook for those desiring a general basic knowledge of nutrition and its problems

Endocrinology Clinical Application and Treatment By August A Werner, M D, Assistant Professor of Internal Medicine, St Louis University School of Medicine Price, \$8.50 Pp 672, with 265 illustrations Philadelphia Lea & Febiger, 1937

As the author suggests in his preface to this book, there is at present a great demand from the medical profession for information on treatment of endocrine conditions He has attempted to meet this demand by supplying a volume, not too long, which deals simply with endocrinology and which, so far as possible, is devoid of frills

The book begins with a clear account of the anatomy of the autonomic nervous system and the relation of this system to the glands of internal secretion There follow chapters which deal with the anatomy and physiology of each of the glands individually, which describe the various clinical features that are encountered

when the function of one or more of the endocrine glands is disturbed and which discuss treatment of endocrine conditions. There are many carefully selected illustrations to illuminate the text. An excellent bibliography appears at the end.

One of the appealing characteristics of this book is that it is not over-pretentious. The hard-headed clinician will enjoy it because it lays chief emphasis on what is known about endocrinology, because it hints so logically about what may be hoped for in the future from endocrinology and because it admits so often and so engagingly that in the light of the present knowledge of this or that complex, no endocrine treatment is of proved value. The student will enjoy it because it is clearly written and well assembled. On the whole it is a good book, heartily to be recommended.

Registro e interpretación de la actividad cardiovascular del lactante normal By Angel S. Segura, M.D. Pp 118. Buenos Aires. Talleres Graficos Alcion, 1937.

This monograph consists of a discussion of the author's experimental studies of cardiovascular function in normal infants by objective methods. He employed the phonocardiograph, electrocardiograph, Frank capsule and other physical instruments for his observations. He made individual and simultaneous records of the heart sound, electrocardiograms and fontanellar, femoral and tibial pulsations in an attempt to observe the time relations between the various phases of the respective cardiovascular activities. The data on the heart sounds of infants led him to conclude that the third heart sound, which is frequently heard in infants, occurs between the first and the second sound and is due to auricular systole. The fontanellar, femoral and tibial pulse waves were studied not only as to time relation to various phases of cardiac activity but as to configuration and variations with respect to age. The phases of the cardiac cycle, heart rate and rhythmicity and the electrocardiogram were observed in an effort to establish a normal and to determine the presence of such correlating factors as age and sex.

Many tables and illustrations are dispersed throughout the book and increase its value. A general summary, which is given in Spanish, French, English and German, is included at the end of the dissertation. A bibliography and a brief index constitute the final pages of the monograph. Segura's presentation should prove of considerable value to those especially interested in cardiovascular physiology.

News and Comment

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation—The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation is now in its fifteenth year. Twenty-six grants were made by this foundation during 1937, eighteen of which were to scientists outside the United States.

Applications for grants to be made during the year 1938-1939 should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, so as to reach him prior to May 1, 1938. There are no formal application blanks. Letters asking for aid should include a definite statement of the qualifications of the investigator, an accurate description of the proposed research, the size of the grant requested and the specific use of the money to be expended. It is highly desirable to include a letter of recommendation from the director of the laboratory or clinic in which the work is to be done.

The purposes for which this fund may be used have previously been mentioned in the ARCHIVES (55 344 [Feb.] 1935).

American Physiological Society—The American Physiological Society will meet with the federated societies at the Lord Baltimore Hotel, Baltimore, March 31 to April 2, 1938. The program includes a consideration of the circulation, the central nervous system, gastrointestinal motility, the choroid plexus, the electrolytes and water balance, endocrinology, the heart, the nerve fibers and reflexes, bile secretion, hepatic lipids and the appetite, the special senses and general physiology, energy metabolism and anoxia. There will be a symposium on the last-mentioned subject on the final day, which will undoubtedly be of considerable interest to physiologists and physicians alike.

A special all expense, low rate tour (\$41.50 and up) will leave from Chicago on Tuesday afternoon, March 29.

For further particulars address Prof. A. B. Luckhardt, the University of Chicago.

Association of American Physicians—The annual meeting of the Association of American Physicians will be held in Atlantic City, N. J., May 3 to 5, 1938.

Correspondence

FOUR LEAD ELECTROCARDIOGRAM

To the Editor —In view of the recent recommendations of the special committee of the American Heart Association on chest leads (Standardization of Precordial Leads, J A M A **110** 395 [Jan 29] 1938, Standardization of Precordial Leads, Supplementary Report, *ibid* **110** 681 [Feb 26] 1938), it seems worth while to revise figure 15 and table 6 which accompanied our recent article on the four lead electrocardiogram (Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, Arch Int Med **61** 241 [Feb] 1938) so that they will conform with the recommendations submitted by this committee for standardizing chest leads

We have been accustomed to taking chest leads at Michael Reese Hospital with the chest electrode in the fourth intercostal space and in the left parasternal line and with the indifferent electrode on the left leg, the connections being arranged so that relative negativity of the precordial electrode causes an upright deflection, in our communications this has been called lead IV. The committee's first report recommended the reversal of the electrodes so that relative positivity of the chest electrode causes an upright deflection. In their second report the lead employing the location of the chest electrode which we have used is designated CF₂. Accordingly, we have revised figure 15 so as to make the following changes: (a) we have called the lead IV which we have been accustomed to use lead IV—old, (b) we have put a plus and a minus sign on the electrocardiogram in stage 1 (normal contour) to designate the direction the deflections would take when the chest electrode became relatively positive and relatively negative with respect to the leg electrode and (c) we have added a new column, which we call lead IV—new (CF₂) to show the appearance of the electrocardiogram with the chest electrode in the position we have employed but with the chest and indifferent electrodes arranged as recommended by the special committee. It will be seen to be a mirror image of lead IV—old. Relative positivity and negativity of the chest electrode with respect to the leg electrode is shown in this column by a plus or a minus sign as in the preceding column.

In this way the reader can correlate the old and the new way of taking chest leads and can obtain the sequential diagrammatic picture of typical anterior and typical posterior infarction when using the old technic and the new technic for taking chest leads. This, we believe, should also serve the useful function of simplifying the transition from the old to the new style of chest leads for cardiologists who have been using the old style. We believe, on the basis of unpublished results, that the appearance of the chest lead will not be materially different when the chest electrode is placed over the apex (IV₁) or in the positions labeled by the committee CF₁, CF₂, CF₃. (We are still not in favor of the apex position, for reasons enumerated in our communication.)

In table 6 we have changed the column dealing with the direction of the deflections in lead IV so that it now expresses the direction of the deflection in this lead in terms of the relative potential of the chest electrode with respect to the leg electrode. Thus this table can now be used with either the old or the new technic.

TABLE 6 (revised)—Classification of Types of Coronary Insufficiency

Type of Myocardial Involvement		Type of Coronary Involvement	Location of Myocardial Involvement	Most Common Type of Electrocardiographic Changes*		Cases Which Illustrate the Type
I Subacute { Definite myocardial infarction	A Uncomplicated or classic forms	Thrombotic occlusion	Anterior infarction	ST ₁ + T ₁ —	QRS ₁ — ST ₄ + T ₄ — or ±	8 cases (fig 1)
			Posterior infarction	ST ₃ + T ₃ —	QRS ₁ ± ST ₁ — T ₁ + +	3 cases (fig 11 to C)
	B Complicated or atypical forms	Sclerotic occlusion	Anterior infarction	ST ₁ — T ₁ —	QRS ₁ — T ₁ ±	7 cases (figs 2 and 3)
			Posterior infarction	T ₃ —	QRS ₁ — or ±	1 case (fig 4D)
II Chronic, progressive or nonprogressive	Fibrosis without infarction	Both arteries occluded	Old posterior with recent anterior infarction	Often like anterior infarction		4 cases (figs 5, 7A and B and 11A)
			Old anterior with recent posterior infarction	Often like posterior infarction		4 cases (figs 61 and B 7C and 11B)
			Multiple small infarcts	Atypical		2 cases (fig 8A and B)
III Acute, transitory	Transitory ischemia	Indeterminate	No infarct visible fibrosis usual	1 Like anterior infarction 2 Like posterior infarction 3 Indeterminate		2 cases (fig 10A and B) 5 cases (fig 9)
			Indeterminate	ST and T deviations variable		2 cases (figs 8C and 10C)

* Inferior number 4 applies to lead CF₂ described in the report of the special committee of the American Heart Association (Standardization of Precordial Leads Supplementary Report, J. A. M. A. 110 681 [Feb 26] 1933) + or — in this lead indicates the relative potential of the chest electrode with respect to the leg electrode

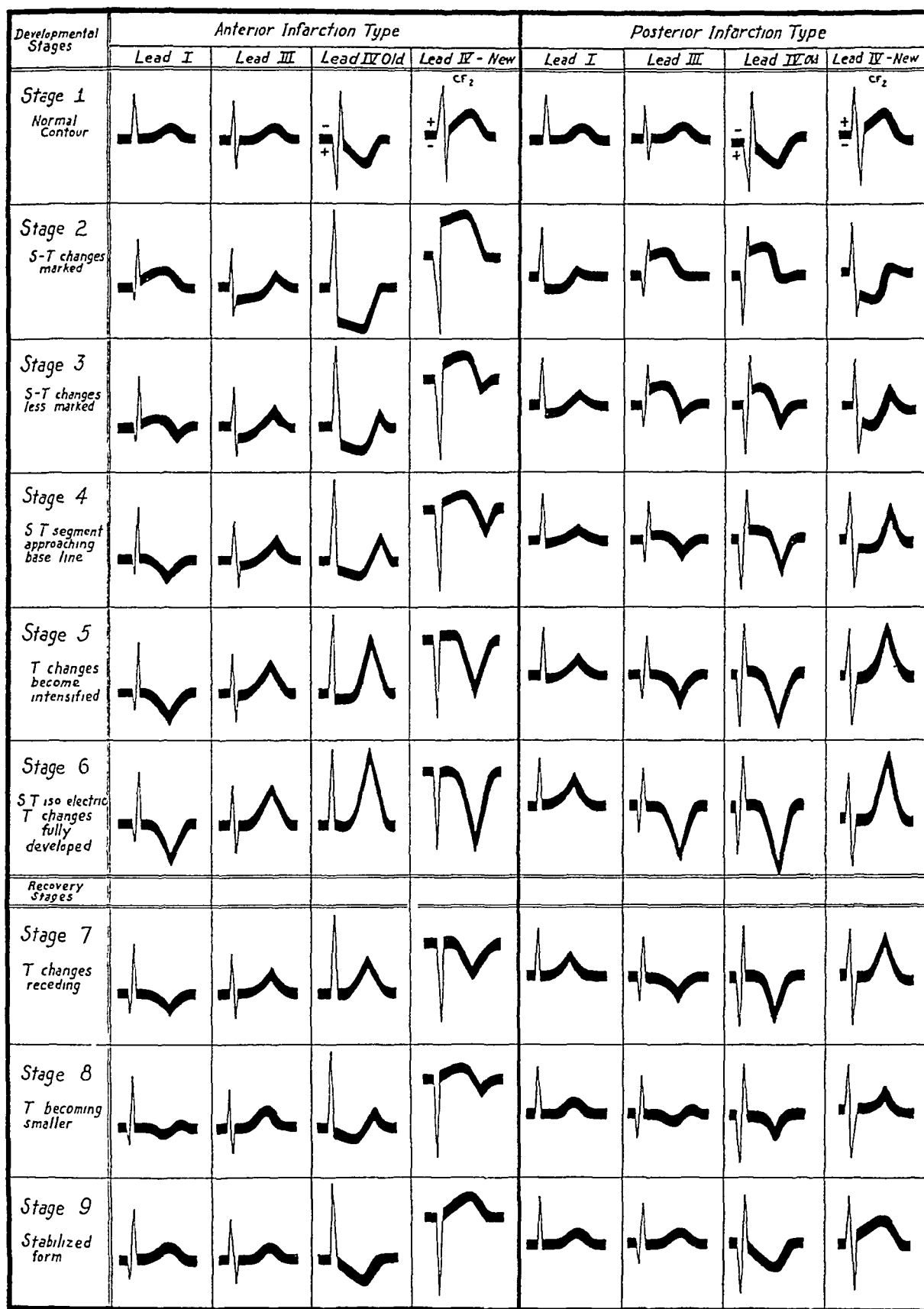


Fig 15 (revised) —Diagrammatic illustration of the classic type of changes usually found in leads I, III and IV in the stages of development of and recovery from uncomplicated infarctions of the anterior and of the posterior wall due to sudden thrombotic closures. In each instance the appearance of lead IV, as we have been taking it heretofore, is shown side by side with the new lead IV—in reality, lead CF₂, according to the recent report of the special committee of the American Heart Association published in *The Journal of the American Medical Association* (Standardization of Precordial Leads, Supplementary Report, J A M A **110** 681 [Feb 26] 1938). In lead IV + and — refer to the relative potential of the precordial electrode with respect to the leg electrode.

We regret that our report was in the process of publication during the time that the special committee of the American Heart Association was considering the standards to be employed for chest leads so that we could not revise our illustrations and data to conform with their report. The present communication should rectify this situation as far as this particular diagram and table are concerned. As regards the other illustrations in our previous reports for which the old technic was used, we recommend that the reader place a mirror above each figure and look at the image in the mirror to obtain the contour of the electrocardiogram which would have been obtained if the recommendations of the special committee had been followed. As regards the text, the reader will need to make the following substitutions: negative for positive, down for up, depressed for elevated, inverted for upright and below the iso-electric line for above the iso-electric line and vice versa in order to revise the text to conform with the recommendations of the special committee.

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ARCHIVES of INTERNAL MEDICINE

VOLUME 61

APRIL 1938

NUMBER 4

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LAURENCE-MOON-BIEDL SYNDROME

ITS RELATION TO THE GENERAL PROBLEM OF RETINITIS PIGMENTOSA

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AND

ROBERT K LAMBERT, M D

NEW YORK

In recent years, with the advent of newer knowledge concerning vitamins, hormones and the autonomic nervous system, many clinicians have shown renewed interest in the problem of the pathogenesis of retinitis pigmentosa. As a result patients with this disease have been gorged with vitamins, plied with hormones and subjected to cervical sympathectomy in an effort to arrest or cure the condition. Without wishing to be therapeutic nihilists, we believe that these efforts have been misguided. This belief has been reenforced by a study of the Laurence-Moon-Biedl syndrome in 2 instances.

In view of the fact that classic examples of the Laurence-Moon-Biedl syndrome are so rare as to be of great interest and are full of significant implications with regard to the polyglandular and retinal manifestations, it is felt that these cases are worthy of report.

REPORT OF CASES

CASE 1—A Z, a 12 year old white Cuban boy, was referred on Aug 9, 1935, to the consultation service at Mount Sinai Hospital. There was no parental consanguinity. One relative on the father's side was said to have had polydactyly. The patient, an only child, was born with six toes on each foot, and the extra toes were removed shortly after birth. His development was apparently normal up to the age of 6 years, when his mother noticed that his vision was poor. At about this time he also began to gain weight rapidly.

Examination—The boy was 4 feet and 11¾ inches (151.8 cm) tall and weighed 136½ pounds (62 Kg). He was short and obese, with a typical feminine type of fat distribution about the breasts and hips and a suprapubic fat pad. The face was rather large. Prominent raphes were on the hard palate. The fingers were tapering. There was a scar of the excised sixth toe on each foot. The penis was small. No pubic hair was present. The median raphe and the corrugations of the scrotum were lacking. The testes had descended. The skin was soft and the hair silky.

From the Consultation Service of the Mount Sinai Hospital and the Neurologic Service of the Montefiore Hospital.

Examination of the eyes gave the following data. In both the left and the right eye, vision, corrected, was 15/20, with -0.75 cyl, axis 180° . External examination showed that the pupillary reactions and muscle balance were normal. The visual fields (fig 1) were markedly contracted in both eyes, in the right more than in the left, but central vision was well preserved. The media were clear, and there were no changes in the lens. The fundus showed a waxy nerve head and thin vessels. There was a sparse but definite deposit of pigment in the periphery of each fundus which was superficially placed and of a "bone-corpusele" type.

The patient showed no gross behavior disturbance and exhibited a rather placid disposition. His mental age according to the Terman revision of the Binet-Simon test was 9 years, giving an intelligence quotient of 70 and placing him in the high-grade moron group. The psychologist described him as a well-mannered boy who showed good cooperation but had slow reactions.

Laboratory Findings—The blood count was normal. Urinalysis showed a faint trace of albumin. The Kahn reaction of the blood was negative. Tests of the blood sedimentation rate and dextrose tolerance gave normal results. The basal metabolic rate was -16 per cent.

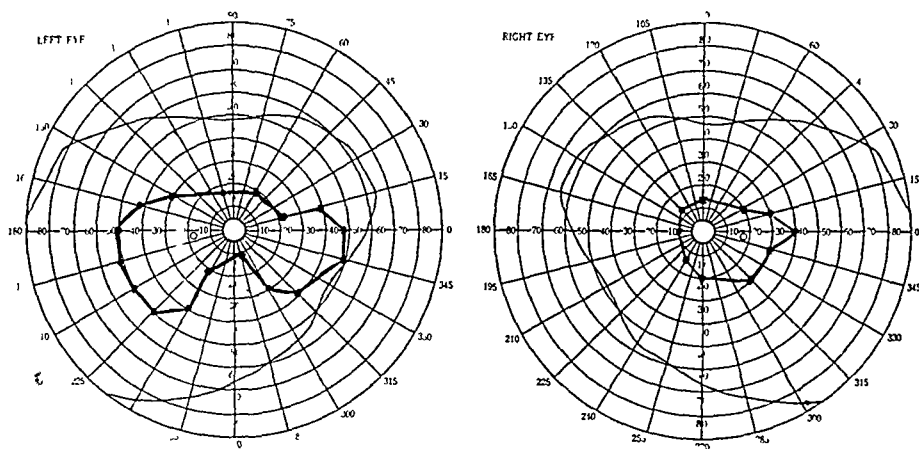


Fig 1 (case 1)—The visual fields were plotted with 5 mm test objects. The color fields were contracted to within 10 degrees of the test object.

A roentgenogram of the skull showed that the sella turcica was normal in size and shape. No erosion of the clinoid processes, no evidence of increased intracranial pressure and no unusual shadows in the cranial vault were observed.

CASE 2—J. R., a 14-year-old Jewish boy, was admitted to the neurologic service of the Montefiore Hospital on June 5, 1934. The parents were born in Poland and were first cousins. The father was unstable and had a short psychotic episode at one time, from which he apparently recovered. A brother of the father had dementia praecox and was in an institution. The mother, who died at the age of 44, was said to have had a cardiac disorder and to have suffered from frequent convulsive seizures for two years prior to her death. After the birth of this son she had a postpartum psychosis and was maniacal for five months. A brother of the mother also had a cardiac disorder and died at the age of 32. The patient's only sibling, a brother 5 years his senior, was normal in all respects except that he was considered to be somewhat below average mentally.

The patient weighed 6 pounds (2,700 Gm) at birth, following breech delivery. He began to walk when $1\frac{1}{2}$ years old and to talk at 2 years, in each respect, about

six months later than his sibling. When he was 2 years of age it was noticed that he did not see well and that he groped about for objects as though blind. When he entered school it was noted that he was mentally retarded, and he was placed in an ungraded class. At the age of 9 he began to put on weight rapidly and soon became obese. The father said that the boy drank a great deal of water about this time and also urinated a great deal, but he was unable to state how long this continued. There was no history of any behavior disturbance.

Examination—The boy was 4 feet and 10 inches (147 cm) tall and weighed 144 pounds (65 Kg). He was short and markedly obese and appeared three or

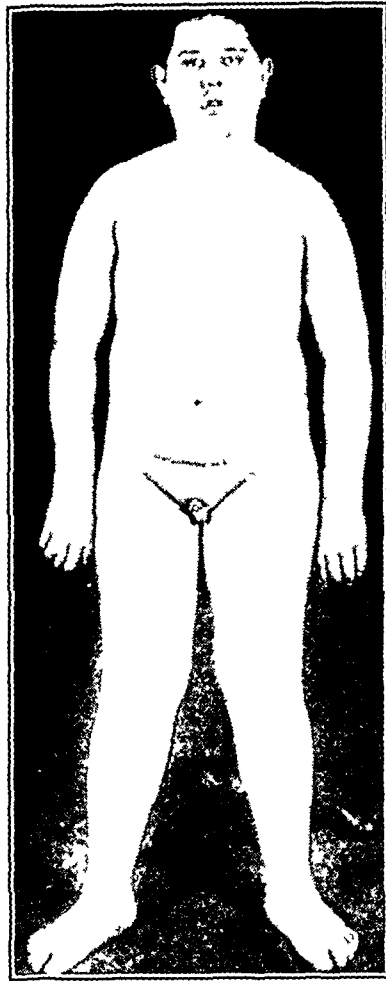


Fig. 2 (case 2) —The appearance of the patient at the age of 14. Note the failure of descent of the right testicle and syndactyly of the second and third toes of both feet. (Figures 2 and 3 were reproduced in the volume by L. Lichtwitz entitled "Pathologie der Funktionen und Regulationen," Leiden, A. W. Sythoff's Uitgeversmaatschappij N. V., 1936.)

four years younger than his stated age (fig. 2). His cheeks were ruddy. He was brachycephalic. The hair was of fine texture. There was no axillary or pubic hair. The mouth was small and the palate high and arched. The teeth slanted inward. Bilateral pes planus and genu valgum were present. The penis was small and undeveloped. The right testis was undescended. The left testis was small and soft. There were striae across the hips. The fingers were short.

and tapering. There was polydactylism of the right hand (fig 3). Syndactylism was present in both feet (second and third toes). Neurologic examination revealed no abnormality except hypotonia. There was a small dimple at the upper end of the gluteal fold which suggested spina bifida occulta, but a roentgenogram of the lower portion of the spine was normal. The blood pressure was 110 systolic and 80 diastolic.

Examination of the eyes showed that vision was markedly reduced, he was able to count fingers at 1 foot (30 cm) with either eye. Vision could not be improved with lenses. There was moderate divergent strabismus. No muscle palsies were noted, but there was a constant coarse nystagmus in all directions. The pupils were markedly eccentric but equal and reacted normally. There were no posterior lenticular opacities. Both nerve heads were pale and vertically oval. The arteries were extremely thin. Around the periphery of the fundus was a scattered deposit of superficial pigment. Although this did not have the typical "bone corpuscle" appearance, the distribution was characteristic of retinitis pigmentosa. There was some disorganization of the pigment in both maculae (fig 4).



Fig 3 (case 2) —Showing the polydactylism of the right hand and the short, tapering fingers.

Attempts at studies of the visual fields were unsuccessful because of the poor visual acuity. Central vision seemed absent bilaterally, and the patient was unable to fixate an object. There was no color vision in either eye.

The patient showed no gross behavior disturbance. He appeared to be mentally defective. His mental age according to the Terman revision of the Binet-Simon test was 7 years and 10 months, giving him an intelligence quotient of 54 and placing him in the low grade moron group. However, the psychologist said that the rating was probably too low owing to the fact that the patient was handicapped by poor vision. This was consistent with the clinical impression.

Laboratory Findings—The blood count was normal. Urinalysis was normal. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid gave a negative Wassermann reaction. The cell count, globulin reaction and gum mastic curve were all normal. The blood sedimentation rate, results of gastric analysis and dextrose tolerance were all within normal limits. Chemical study of the blood showed calcium, 10.8 mg, phosphorus, 4.6 mg, cholesterol, 201 mg,

serum protein, 7.4 Gm (albumin, 4.2 Gm, globulin, 3.2 Gm), sugar, 92 mg, and urea nitrogen, 11.1 mg, per hundred cubic centimeters

The basal metabolic rates on various occasions ranged between —17 and —31 per cent

Roentgenograms of the skull and sella turcica were normal. The long bones and epiphyseal centers were normal for the patient's age. In the region of the fourth finger of the right hand there was an extra digit, consisting of a rudimentary metacarpus and three well formed phalanges.

Course—Anterior pituitary extract parenterally and desiccated thyroid orally were administered without demonstrable change in the patient's condition, either subjectively or objectively. The visual acuity and the appearance of the fundi did

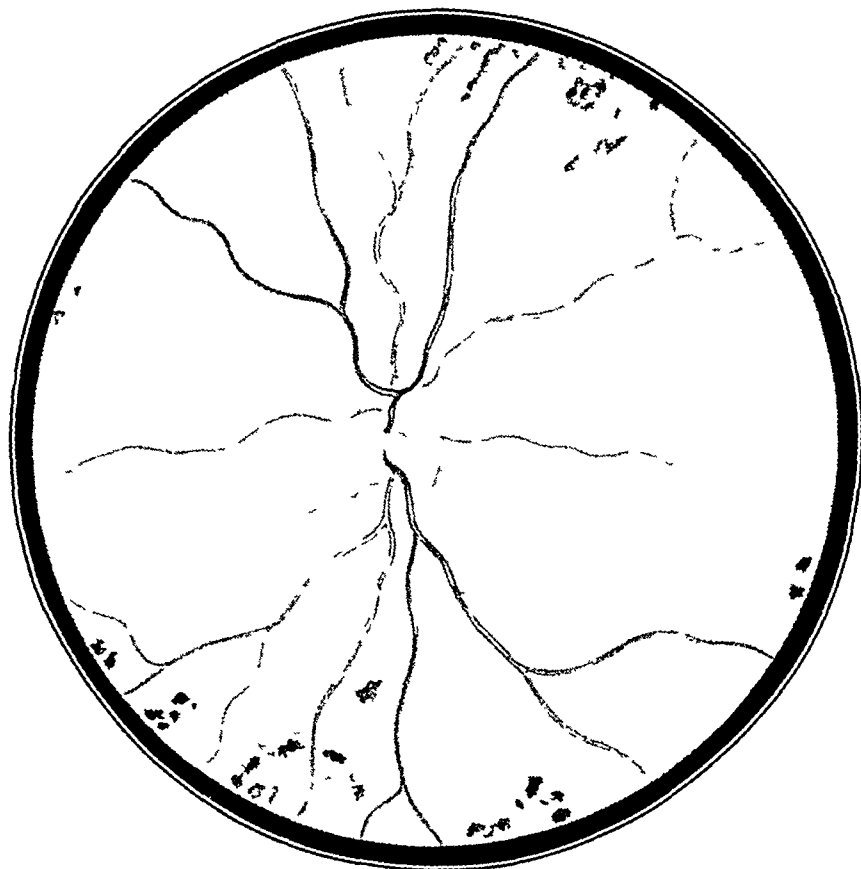


Fig. 4 (case 2)—The appearance of the fundus. Note the pale nerve head, narrow vessels, atrophy in the macula and pigmentary deposits in the periphery.

not change. A few sparse hairs appeared in the pubic region but not in the axillae or over the trunk. In July 1937 the patient was 5 feet and 2½ inches (159 cm) tall and weighed 175 pounds (79.5 Kg).

Summary—Both of these patients presented a classic example of the Laurence-Moon-Biedl syndrome. Retinal degeneration, adiposity, genital dystrophy, polydactyly and mental deficiency were observed in each instance. A family history of polydactyly was present in the first case and consanguinity of the parents in the second. The first patient was an only child. The second patient was one of two brothers, the

other boy was said to be normal except for possible mild mental deficiency. The fundus in both cases was fairly characteristic of retinitis pigmentosa, but central vision was well preserved in the first case. In the second, it was markedly impaired, and nystagmus was present. The adiposity and genital dystrophy in both instances were of the so-called hypopituitary type seen in the Fohlich syndrome. The first patient was born with a sixth toe on the lateral aspect of each foot. The polydactyly of the second patient consisted of an extra digit situated posteriorly in the region of the fourth finger of the right hand, in addition, there was syndactyly of the second and third toes of both feet. Mentally both patients belonged in the moron group, their mental ages being approximately 9 and 8 years, respectively. In neither instance was there any gross behavior disturbance. The laboratory studies in both cases revealed no abnormality except a low metabolic rate. Roentgenograms of the skull and sella turcica were normal. Endocrine therapy was employed in the second case without producing discernible improvement.

HISTORICAL REVIEW

Although the familial occurrence of atypical retinitis pigmentosa, stunting of growth, adiposity, hypogenitalism and mental deficiency was first described by Laurence and Moon¹ in 1866, it was not until fifty-four years later, in 1920, that it was recognized by Bardet² as constituting a distinct clinical syndrome. Bardet noted that his patient also showed polydactyly, and he included this characteristic as part of the syndrome. He failed, however to appreciate mental deficiency and the familial occurrence as essential parts of the syndrome. Biedl,³ two years later, in reporting 3 cases, recognized the familial occurrence, noted the occasional concomitance of other malformations (atresia and deformities of the skull) and pointed out that there were no evidences of cerebral tumor or increased intracranial tension. Solis-Cohen and Weiss,⁴ in 1925, reported 4 cases, drew attention to the original description by Laurence and Moon and suggested the name Laurence-Moon-Biedl syndrome, by which the condition has since been generally known. That it might with equal justice have been named the Laurence-Moon-Bardet syndrome has been commented on by several writers.

In the past twelve years a number of papers have appeared on the subject, and almost 100 cases have now been described, including 38

1 Laurence, J. Z., and Moon, R. C. *Ophth. Rev.* **2**: 32, 1866.

2 Bardet, G. *Sur un syndrome d'obésité congénitale avec polydactylie et rétinite pigmentaire*, Thèse de Paris, no. 470, 1920.

3 Biedl, A. *Deutsche med. Wchnschr.* **48**: 1630, 1922.

4 Solis-Cohen, S., and Weiss, E. *Am. J. M. Sc.* **169**: 489, 1925.

reports of cases which were discovered by Raab⁵ in a search of the literature prior to 1924. In all, however, not more than 50 cases in which the complete syndrome was shown have been described, the remainder being cases in which there was a partial syndrome or in which the diagnosis was doubtful. Reilly and Lissner⁶ in their comprehensive survey and summary of the literature found reports of a total of 77 cases, and in only 25 cases was the complete syndrome presented. In 10 others the syndrome was considered as questionably complete. In 26 cases there was only part of the syndrome, and in 16 cases the diagnosis was doubtful. More recently, Cockayne, Krestin and Sorsby⁷ have contributed an excellent authoritative study.

CLINICAL DATA

The complete syndrome as it is known today consists of six cardinal signs—obesity, retinitis pigmentosa, mental deficiency, genital dystrophy, familial occurrence and polydactylism, in the order of frequency. Obesity is present in practically all the cases in which there is no doubt as to the diagnosis, retinitis pigmentosa and mental deficiency, in over 90 per cent, genital dystrophy and familial occurrence, in about 80 per cent, and polydactyly, in about 60 per cent. Other associated signs which are less frequently present are shortness of stature, syndactylism, nystagmus, deafness, atresia ani, genu valgum, pes planus, microcephaly, oxycephaly, congenital heart disease and choreiform movements. The parents are reported as healthy in the majority of cases, but consanguinity was noted in more than a third of the cases in which it was looked for. The syndrome has been described in representatives of almost all races and nationalities. According to Cockayne and his co-workers, there is a genuine preponderance of males over females, in the proportion of 61 to 40.

DIAGNOSIS

It should be emphasized that it is not necessary to have all six cardinal signs present in order to make a presumptive diagnosis of the Laurence-Moon-Biedl syndrome. The association of retinitis pigmentosa, obesity and genital dystrophy is in itself enough to raise the suspicion that one is dealing with an allied condition or a partial syndrome. Generally speaking, one would hesitate to make the diagnosis in the absence of retinal degeneration. Weiss⁸ however, has described as representing

5 Raab, W. *Wien Arch f inn Med* **7**:443, 1924.

6 Reilly, W. A., and Lissner, H. *Endocrinology* **16** 337, 1932.

7 Cockayne, E. A., Krestin, D., and Sorsby, A. *Quart J Med* **4** 93, 1935.

8 Weiss, E. *Am J M Sc* **183** 268, 1932.

variants of the Laurence-Moon-Biedl syndrome the cases of 2 sisters who showed adiposity, mental deficiency, genital dystrophy and nerve deafness. He said he considered the nerve deafness as an equivalent of or substitute for retinal degeneration and pointed out that these disorders are not infrequently associated. We have encountered in the past year several patients with adiposity, genital dystrophy and a peculiar waxy appearance of the optic disks, and we believe that these cases also are allied to the Laurence-Moon-Biedl group, despite the absence of polydactyly or typical retinal pigmentary degeneration. This group of cases will be described in a separate paper. It need only be mentioned here that it is of importance to distinguish such conditions from other types of adiposogenital dystrophy with which they might be readily confused. The absence of any roentgenologic evidence of an intrasellar or suprasellar pathologic condition and the appearance at an early age of optic pallor, atypical retinal changes, narrowing of the retinal vessels and gross impairment of vision without increased intracranial pressure or other adequate cause are the chief features which set these cases apart from cases of other forms of adiposogenital dystrophy.

PATHOGENESIS

The pathogenesis of the syndrome has been the subject of considerable discussion. The earlier writers, in describing these cases, held the pituitary gland responsible. Biedl,³ in 1922, finding the sella turcica normal in his 3 cases, rejected the hypophysial theory and said he considered the disease as due to a diencephalic lesion. In 1924 Raab⁵ suggested that a high or massive dorsum sellae was causing pressure on the infundibular stalk, thus disturbing the passage of secretion from the posterior lobe of the hypophysis to the floor of the third ventricle. Raab's views are no longer considered tenable. Ornstein,⁹ in 1932, suggested that the concomitant association of obesity, genital dystrophy, retinitis pigmentosa and mental deficiency is due to a developmental defect of the ectopic zone of the prosencephalon, since the hypothalamus, infundibulum, optic chiasm, retina and end brain all take origin from this zone. He said he considered the skeletal defects (such as polydactylism) the result of accidental coupling of defective somatic genotypic characters. In 1935 Cockayne and his co-workers⁷ and Jenkins and Poncher,¹⁰ writing independently, raised the legitimate objection to Ornstein's theory that the coupling of so rare an anomaly as polydactyly occurred too frequently to be adequately explained on an accidental basis. They suggested, instead, that the syndrome is due to mutation of

9 Ornstein, A. M. *Am J M Sc* **183** 256, 1932.

10 Jenkins, R. L., and Poncher, H. G. Pathogenesis of Laurence-Biedl Syndrome, *Am J Dis Child* **50** 178 (July) 1935.

two genes in the same chromosome and is inherited as an autosomal recessive characteristic. Priority for this suggestion is given by these authors to Rieger and Trauner¹¹

Cockayne has pointed out that the polydactyly and other skeletal abnormalities are due to a mesoblastic defect, while the rest of the syndrome is dependent on a defect in the prosencephalon, which is epiblastic, and that it is therefore highly unlikely that mutation of a single gene is responsible for the entire syndrome. In cases in which polydactyly does not occur, however, and in cases of a partial syndrome of the type we have mentioned, in which the defect is entirely ectodermal, substitution of a single recessive gene could account for the disease.

Recently Macklin,¹² in a detailed genetic study based chiefly on Cockayne's data, stated the conclusion that the complete syndrome "may be dependent upon two factors, both of which are necessary before the disease becomes evident, one of which is dominant and autosomal, and the other sex-linked recessive."

PATHOLOGIC PICTURE

Until one year ago no case of the Laurence-Moon-Biedl syndrome had been studied histologically, although Bauer¹³ had reported the normal gross appearance of the brain in 1 case. He neglected, however, to make microscopic studies.

In 1936 van Bogaert and Borremans¹⁴ published the first detailed anatomic study of the brain of 1 of these patients. Unfortunately, permission was evidently not obtained for examination of any other organs, since no mention is made of them in the report. The cerebrum, according to the authors, was entirely normal except for small areas of hyaline necrosis in the hypophysial stalk. These were considered of no specific clinical physiopathologic significance, since they are seen in various other unrelated conditions. The pituitary gland and hypothalamus were normal both grossly and microscopically, as was the remainder of the central nervous system. There was hyperostosis frontalis interna in the anterior cranial fossa. "These negative findings," according to the authors, "permit one to exclude with certainty the theory which considers that a malformation or trauma at birth, in the diencephalo-hypophyseal region, is at the basis of the retino-endocrine syndrome of Laurence-Bardet." It is apparent that further postmortem studies of this syndrome will be necessary before anything like a clear picture of the pathologic basis emerges. It is to be hoped, moreover, that such

11 Rieger, H., and Trauner, R. *Ztschr. f. Augenh.* **68** 235, 1929.

12 Macklin, M. T. *J. Hered.* **27** 97, 1936.

13 Bauer, cited by van Bogaert and Borremans¹⁴.

14 van Bogaert, L., and Borremans, P. *Ann. de med.* **39** 54, 1936.

studies will include an examination of other glands of internal secretion besides the hypophysis

OCULAR FINDINGS

A disturbance in vision, particularly night blindness, is frequently the first symptom to attract attention in these cases. This may occur early in life. Nystagmus may be present, in the form of coarse searching movements, depending on the loss of central vision.

In all the original cases described by Laurence and Moon in an ophthalmologic journal, defective vision and the night blindness characteristic of retinitis pigmentosa were marked. Ophthalmoscopically, scattered areas of pigmentary degeneration were visible in the periphery of the fundi, generally along the course of the retinal vessels. There was no definite atrophy of the optic nerve. In almost all the subsequently described cases some form of retinal degeneration was present. The type of retinal change, however, has varied considerably. Clay¹⁵ has stated that in only 15 per cent of the cases has the typical picture of retinitis pigmentosa been described. By far the greatest number have been recorded as "atypical." In most of the latter cases there have been peripheral pigmentary lesions in varying degrees, with sparing of the macula. In some there has been mild to marked choroidal atrophy, in still others, macular lesions similar to those seen in cases of cerebro-macular degeneration. Several authors have described cases of retinitis pigmentosa sine pigmento, while Lissner¹⁶ described a case of retinitis punctata albescens (a condition which is allied to retinitis pigmentosa and in which there are pigment deposits, vascular changes and numerous small scattered white spots).

A fairly uniform narrowing of the retinal vessels is practically always present, as is a waxy pallor of the nerve head. Various other ocular findings, such as posterior cortical cataract, strabismus and axial myopia, have also been described in connection with this syndrome.

The pathogenesis of the retinal degeneration in these cases is of great interest, particularly in its application to the broad problem of idiopathic retinitis pigmentosa. The same theories have been proposed to account for both types, although because of the limited number of cases of the Laurence-Moon-Biedl syndrome, the therapeutic attempts in these cases have been fewer. Ornstein⁹ said he was of the opinion that efferent fibers of the optic nerve, controlling chemical changes and movement of pigment in the retina, had been disturbed by a chiasmal defect. Other authors have proposed retinal vascular disease, either primary or secondary to cervical sympathetic dysfunction, vitamin or hormone deficiencies and other possibilities. None of these theories has ever been

15 Clay, G. E. *Tr. Am. Ophth. Soc.* **31** 274, 1933

16 Lissner, H. *Endocrinology* **13** 533, 1929

substantiated in any way. We believe that the evidence obtained from the cases of the Laurence-Moon-Biedl syndrome points to the conclusion that the retinal degeneration, like the other aspects of the syndrome, is an inherited chromosomal factor which is latent from the moment of conception. In this connection it is of interest to note the overwhelming evidence in favor of the hereditary origin of retinitis pigmentosa, presented as early as 1907 by Nettleship¹⁷ in his classic monograph on this subject. He investigated a series of 1,000 families encompassing 1,700 cases. In fully 50 per cent of these cases definite evidence of inheritance or of parental consanguinity was present, and Nettleship stated the opinion that if in the remaining 50 per cent of cases a thorough investigation had been made, the percentage would have been

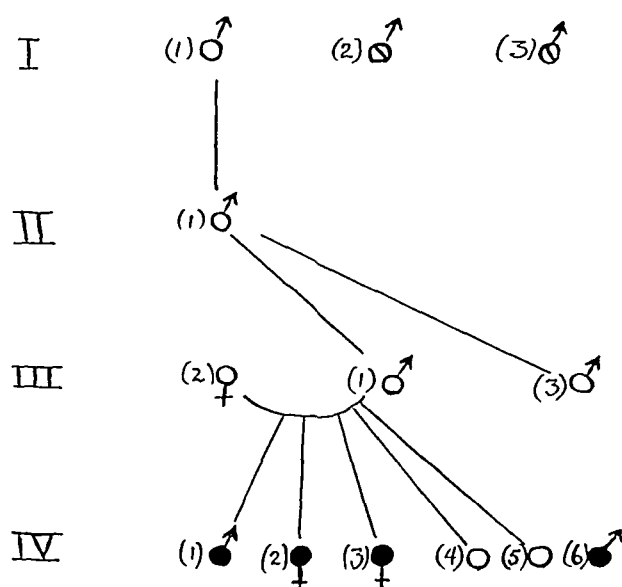


Fig. 5—The family tree presented by Nettleship,¹⁷ showing transmission of retinitis pigmentosa and other anomalies. IV 4 and 5 each represents a group of 4 siblings, the first having died in infancy and the others being normal. IV 6 is the child of III 3.

even higher. In support of this thesis he presented a number of pedigrees, one of which in particular is of extraordinary interest as regards the problem under discussion and deserves reproduction (fig. 5).

In generation I, 1 was perfectly normal, but 2 and 3 were a deaf-mute and an idiot, respectively. The offspring of I₁ in the second and third generations were all normal. However in generation IV, of 11 children, 4 died young, 4 were normal and 3 were idiots with advanced retinitis pigmentosa. In addition, IV₁ was partly deaf and had six toes on each foot and six fingers on the left hand, and IV₃ had six toes on each foot. Moreover, a paternal first cousin, IV₆, was a deaf-mute

17 Nettleship, E. Roy. London Ophth. Hosp. Rep. **17** 151, 1907-1908.

and blind. In emphasizing the importance of careful genetic studies, which this pedigree exemplifies, Nettleship pointed out, first, that all the diseased offspring were descended from I_1 , who was normal, second, that the inheritance was discontinuous for two generations, and finally, that if I_2 , I_3 and IV_6 "had not been included in the history (and such omission might easily have occurred) the case could have been claimed as showing the absence of heredity."

Two other facts mentioned by Nettleship in his valuable study have a bearing on the problem under discussion. One is that of 1,381 patients with retinitis pigmentosa whose sex was noted, 845 were males and 536 females, a ratio of 61:39, which corresponds almost exactly with the ratio arrived at by Cockayne⁷ in cases of the Laurence-Moon-Biedl syndrome.¹ The other is that fully as many variations occur in the ophthalmoscopic picture of so-called idiopathic retinitis pigmentosa as have been described in the Laurence-Moon-Biedl syndrome. The atypical nature of the retinal degeneration in the latter syndrome, therefore, in no way means that it is unrelated to the idiopathic type. On the contrary, the aforementioned evidence seems to favor strongly the conclusion that the two types of retinal degeneration are closely allied. In this connection it may be noted that Wibaut¹⁸ has differentiated two types of retinitis pigmentosa: a dominant type, which is almost never associated with nerve lesions, and a recessive type which is associated with deafness and other types of involvement of the central nervous system.

If further evidence were required to indicate the primary degenerative nature of retinitis pigmentosa and to disprove the theory that it is of vascular origin, Verhoeff's excellent histologic study would remove all doubts. Verhoeff¹⁹ has proved conclusively that degeneration of the retinal neuro-epithelium is the primary lesion in retinitis pigmentosa and that such vascular changes as occur are due to secondary thickening of the vascular walls by the increased proliferation of glial tissue.

LABORATORY STUDIES

Laboratory studies have not revealed any consistent abnormalities. A low basal metabolic rate is the most frequent finding occurring in over 60 per cent of the cases. Dextrose tolerance is generally normal, with some cases of moderately increased or decreased tolerance. Chemical studies have shown a uniformly normal picture. Recently Klenerman²⁰ reported 2 cases in which the calcium content of the serum

18 Wibaut, F. *Klin Monatsbl f Augenh* **87** 298, 1931.

19 Verhoeff, F. H. *Microscopic Observations in a Case of Retinitis Pigmentosa*, *Arch Ophth* **5** 392 (March) 1931.

20 Klenerman, P. I. *J Neurol & Psychopath* **15** 329, 1935.

was high. Both patients, however, were elderly women, aged 72 and 40 respectively, and it is possible that other factors were involved in the disturbed calcium metabolism. Serologic studies have shown a negative Wassermann reaction of the blood in practically all instances.

ROENTGEN STUDIES

Roentgenographic studies likewise have shown no consistent changes. The sella turcica in most of the cases in which it was examined was essentially normal, with an equal number of cases in which it was larger or smaller than normal. The high or massive dorsum sellae, on which Raab placed so much significance, has been observed in only a few cases. Studies of the long bones have revealed normal nuclear osteogenesis in the majority of instances.

TREATMENT

The results of treatment in these cases have, on the whole, not been encouraging, although individual authors have published promising reports. In most cases some form of endocrine therapy has been employed, usually a combination of thyroid and pituitary extract. In the case of females ovarian therapy has also been added. The symptom which seems to be most frequently helped is the obesity, which responds somewhat to the use of thyroid. Occasionally, too, after mixed endocrine therapy, these patients seem to show better muscle tone and increased animation, which makes them appear brighter mentally. It is highly doubtful, however, whether any improvement in the basic mental deficiency ever occurs. Of interest is the fact that a number of writers claim to have observed definite improvement in vision after endocrine therapy (Bernhardt,²¹ Boenheim,²² Beck,²³ and Reilly and Lissei⁶). In most of these cases, however, the improvement was limited and not correlated with objective improvement in the retinal pathologic condition. Other authors (de Schweinitz,²⁴ Solis-Cohen,⁴ and Reilly and Lissei⁶) have claimed to have arrested the failing of vision as a result of therapy, but these conclusions may be questioned, in view of the fact that arrest of failing vision occurs in these cases spontaneously. Surprisingly, there are no reports of any striking improvement in the genital dystrophy, although one would expect that endocrine therapy might be particularly useful in this respect. In view of the numerous favorable reports appearing in recent years concerning the use of the gonadotropic principle of the urine of pregnant women in cases of undescended testicles, it is possible that such therapy vigorously

21 Bernhardt, H. *Ztschr f klin Med* **107** 488, 1928

22 Boenheim, F. *Endokrinologie* **4** 263, 1929

23 Beck, H. *Endocrinology* **13** 375, 1929

24 de Schweinitz, G. *Tr Ophth Soc U Kingdom* **43** 90, 1923

employed, might be of value for the genital dystrophy in the Laurence-Moon-Biedl syndrome

As regards the polydactylism, of course, surgical treatment is the only recourse

COURSE

In all the cases originally described by Laurence and Moon paraplegia eventually developed. This development, however, appears to have been peculiar to this family only and has not been described in any of the subsequent cases. In most of the cases the condition seemed to have been arrested in childhood, and there was little or no subsequent progression in the symptoms. Retinitis pigmentosa rarely progresses to complete blindness. Kleneman's case (that of a woman of 72) shows that the patient may reach an advanced age. Occasionally a reactive behavior disturbance develops.

SUMMARY

Two classic examples of the Laurence-Moon-Biedl syndrome are described.

A brief survey is given of the present information regarding this condition.

The weight of evidence points to the fact that the pigmentary degeneration of the retina in the Laurence-Moon-Biedl syndrome is a congenital anomaly dependent on an inherited chromosomal factor. We believe that this is a link in the chain of evidence pointing toward the congenital nature of the usual form of retinitis pigmentosa.

Permission to report these cases was granted by Dr. Jorge Muniz, of Habana, and Drs. George Baehr and S. Philip Goodhart, of New York.

METABOLISM OF VITAMIN C IN RHEUMATOID ARTHRITIS

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On the basis of the occurrence of gross and microscopic changes in the articular tissues of guinea pigs subjected to subacute or chronic scurvy, either alone or in combination with infection, we made the suggestion that vitamin C deficiency may be a significant contributory mechanism in the etiology of some cases of rheumatoid or atrophic arthritis¹ Brief but suggestive clinical evidence was presented at that time Subsequently we have endeavored to investigate the problem thoroughly in the clinic Detailed dietary histories were taken in as many cases as possible What we consider to be a deficient intake of vitamin C has been a common though not universal finding A detailed analysis of these records will be made and published later

The belief that nutritional factors may be important in this disease is not new Many writers have stressed the importance of nutrition Hall² said "We are constantly seeing patients with severe arthritis, who for months or years have been eating inadequate or deficient diets

Read before the American Rheumatism Association, Atlantic City, N J, June 7, 1937

From the Arthritis Clinic and the Division of Pathology and the Division of Medicine, the University of California Medical School

This investigation was supported by the Christine Breon Fund for Medical Research and by the California Fruit Growers' Exchange Hoffmann-LaRoche, Inc, furnished supplies of vitamin C

1 Rinehart, J F, Connor, C L, and Mettier, S R Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, *J Exper Med* **59** 97, 1934 Rinehart, James F Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis II Rheumatoid Arthritis, *Ann Int Med* **9** 671, 1935

2 Hall, F C Treatment of Arthritis, *Am Med* **35** 367 1929

In such cases, the diet has been the depleting factor " Rowlands³ and Fletcher and Graham⁴ have presented indirect evidence that vitamin B deficiency may operate in the etiology of rheumatoid arthritis. The evidence is based essentially on the frequent observation of atony of the musculature of the colon. Fletcher and Graham gave patients high vitamin diets with particularly generous amounts of vitamin B and observed improvement in the tone of the bowel and frequently much clinical benefit. It is not improbable that vitamin B deficiency states indirectly contribute to the development of arthritis. Nutritional inadequacies are likely to be multiple. Vitamin B deficiency appears to act largely through limitation of the voluntary consumption of food by impairment of appetite. In this way an inadequate intake of vitamin C may follow in its wake, particularly if the selection of food does not include the richer sources of this factor.

A second routine observation in our study has been the determination of the capillary strength by the Dalldorf method⁵. This has been considered an index of "latent scurvy". We realize that there are severe limitations to this method and that many factors other than vitamin C deficiency diminish the capillary resistance. However, it is of significance that we have found the capillary strength almost uniformly and significantly lowered in the atrophic type of arthritis. More recently, particular attention has been directed to the condition of the gums. Swain's⁶ early observation was that in cases of rheumatoid arthritis "the gums are spongy and the teeth decay easily. The mouth resembles that of a scurvy patient". We wish to redirect attention to the prevalence of such gingival changes in this disease. Although it is not invariable, it is remarkably common to find reddened, retracted and edematous gums which are prone to bleed. We do not believe that such a condition can be ascribed to the effect of infection alone. Most students of this disease know how frequently these gingival changes are seen and how often a mouth is encountered from which the teeth have been extracted because of decay or "pyorrhea". It involves no unusual exercise of the imagination to regard the gums as in some respects analogous to the synovial and periarticular tissues. Both are soft tissues applied to dense structures, and both are subjected to repeated trauma. If the synovial membrane is in a boggy, toneless, edematous state and its vessels are unduly fragile and permeable, it (as the gums) may be expected to bleed on

3 Rowlands, M. J. Rheumatoid Arthritis. Is It a Deficiency Disease? *Proc Roy Soc Med* **20** 41, 1927

4 Fletcher, A. A., and Graham, D. The Large Bowel and Chronic Arthritis, *Am J M Sc* **189** 91, 1930

5 Dalldorf, G. A Sensitive Test for Subclinical Scurvy, *Am J Dis Child* **46** 794 (Oct) 1933

6 Swain, L. T. Atrophic Arthritis, *Rhode Island M J* **6** 51, 1923

ooze plasma and, with the deposition of fibrin, to form a bridge for the growth of granulation tissue and extension of a pannus into the articular cavity. Further, such tissues would be predisposed to bacterial localization. If the strength of the capillaries of the skin is reduced in rheumatoid types of arthritis, it is reasonably safe to assume that other capillaries are fragile and hyperpermeable. While such considerations may be somewhat "imaginative," we do not believe them to be unreasonable.

The recent chemical identification of vitamin C and the formulation of methods for assay of its content in foods, urine, tissues and blood have afforded a more direct and perhaps more scientific method of approach to the problem.

We⁷ have previously reported on work confirming the observations of Farmer and Abt⁸ that the vitamin C level of the blood plasma is an accurate index of the immediate nutritive state of a person relative to vitamin C and that in "normal" persons it parallels the intake. We have briefly recorded the finding of low vitamin C values in rheumatoid arthritis⁹. The present report represents an extension of this study.

METHODS

With rare exceptions all specimens of blood analyzed for vitamin C were drawn during the fasting or postabsorptive state. This we consider essential for satisfactory comparative data. The analytic method employed was that originally reported by Farmer and Abt,⁸ in which the blood plasma is deproteinized with tungstic acid and the filtrate titrated with 2, 6-dichlorophenolindophenol. Determinations were made promptly, and due caution was exercised for prevention of oxidation. This method we have found to be reliable and accurate.

CASES STUDIED

The data of this report include observations on 120 medical students as "normal" controls, 26 patients with more or less classic rheumatoid arthritis and 29 patients with less classic arthritis of the rheumatoid type. All the patients exhibited some evidence of activity of the rheumatic process and were seen subsequent to January 1936. In addition, there were 13 patients with gonorrheal arthritis and 12 with hypertrophic arthritis.

PLASMA VITAMIN C IN CONTROLS

The "normal" group showed values for the vitamin C content of the plasma ranging from 0.22 to 1.45 mg per hundred cubic centimeters,

7 Greenberg, L. D., Rinehart, J. F., and Phatak, N. M. Studies on Reduced Ascorbic Acid Content of the Blood Plasma, *Proc. Soc. Exper. Biol. & Med.* **35** 135, 1936.

8 Farmer, Chester J., and Abt, Arthur F. Ascorbic Acid Content of Blood, *Proc. Soc. Exper. Biol. & Med.* **32** 1625, 1935.

9 Rinehart, J. F., Greenberg, L. D., and Baker, F. Reduced Ascorbic Acid Content of Blood Plasma in Rheumatoid Arthritis, *Proc. Soc. Exper. Biol. & Med.* **35** 347, 1936.

with an average of 0.7 mg. The individual distribution for this group, contrasted with that for the arthritic patients, is shown in chart 1. It should be pointed out that the value 0.7 mg. is an average and probably falls below what should be considered optimal. Our present opinion remains essentially as previously reported,⁷ i. e., that during fasting cevitamic acid levels of the plasma below 0.7 mg. are probably suboptimal. Levels ranging between 0.7 and 0.9 mg. appear to be adequate, and levels below 0.5 mg. must be considered low. Several of the controls showing the lowest vitamin C levels presented findings, such as gingivitis and lowered capillary strength, that might be considered as evidence of vitamin C deficiency.

PLASMA VITAMIN C IN ARTHRITIS

It will be seen from chart 1 that the patients with active true rheumatoid and rheumatoid types of arthritis exhibited initial vitamin C values

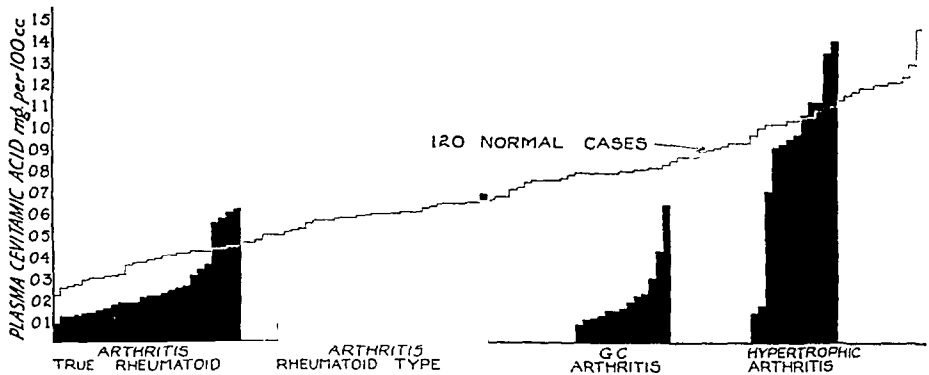


Chart 1—Distribution curve of the cevitamic acid content of the plasma of normal controls and of patients with arthritis. G. C. indicates gonococcic

of the blood plasma that were uniformly in a strikingly low range. For the 26 patients with more or less classic rheumatoid arthritis, the range was from 0.09 to 0.68 mg. per hundred cubic centimeters, with an average of 0.23 mg. Ninety-three per cent of the values were below 0.5 mg., and 76 per cent were below 0.3 mg. (i. e., at markedly low levels). Essentially similar data apply to the 29 patients with arthritis classified as of "rheumatoid type." Interestingly, the smaller series of patients with gonorrheal arthritis also showed evidence of vitamin C deficiency. The significance of this will be considered presently. The distribution for patients with hypertrophic arthritis was above that for the normal controls.

Chart 2 shows a distribution diagram of the cevitamic acid values for 120 normal controls contrasted with those for the 55 patients with active rheumatoid or rheumatoid types of arthritis. The average value

for the controls was 0.7 mg per hundred cubic centimeters and for those with arthritis, 0.24 mg. Eighty-nine per cent of those with arthritis (rheumatoid and rheumatoid types) showed values below 0.5 mg, and 74.5 per cent showed values below 0.3 mg. For the control series only 26.6 per cent of the values were below 0.5 mg, and 4.2 per cent were below 0.3 mg. Without doubt some of the controls had a suboptimal or inadequate intake of vitamin C. It should be pointed out that the great majority of the patients with rheumatoid arthritis, although showing clinical or laboratory evidence of activity, were ambulatory and were seen in the outpatient department. They were not suffering from acute intoxication, and only a few had suffered any recent acute illness. There

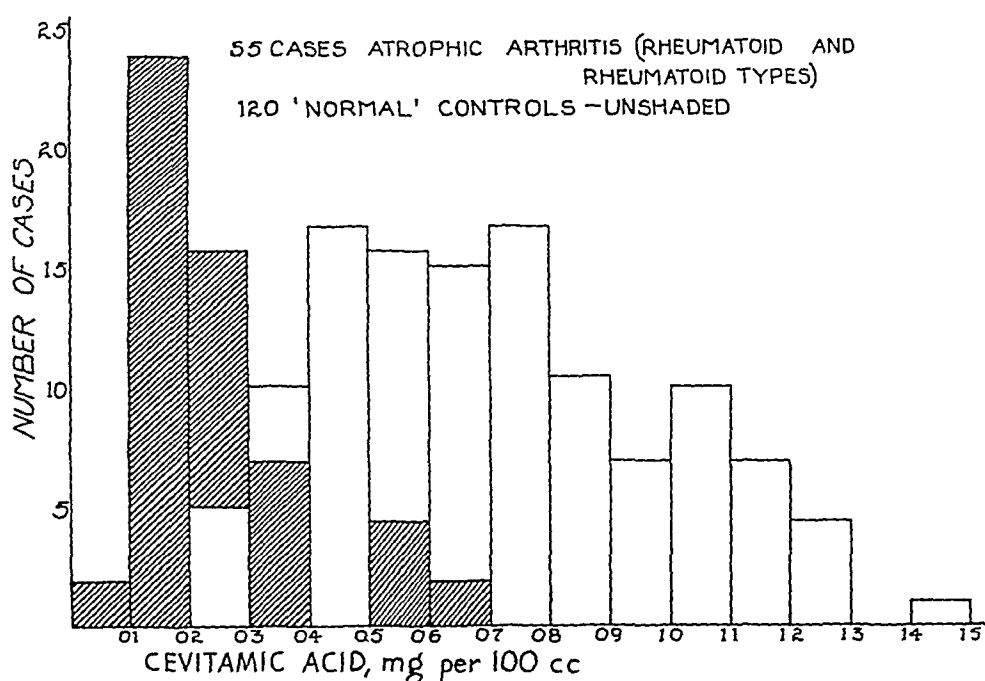


Chart 2—Distribution diagram of the values for the cevitic acid content of the plasma

is no reason to believe that the values recorded for the vitamin C content of the blood did not represent habitual levels.

RESPONSE OF CONTROLS AND ARTHRITIC PATIENTS TO SUPPLEMENTARY INTAKE OF VITAMIN C

In certain of the controls and of the patients with arthritis it was possible to study the response of the blood plasma levels to extra supplements of vitamin C. Thirteen of the controls who showed initially low values for the cevitic acid content of the blood were given a daily oral supplement of 100 mg of vitamin C, and subsequent deter-

minations were made. These cases are represented graphically in chart 3. They not only afford convincing evidence that the vitamin C content of the plasma parallels the intake but for the most part show surprisingly prompt rises to levels within the normal range. The 2 patients who showed the lowest initial plasma levels (P F and F O D) and who exhibited delayed rises were probably suffering from subclinical deficiency. Both showed gingival changes, lowered capillary strength and a dietary history rated as low in vitamin C. The average response of this control group is indicated by the dotted line. This line is superimposed as a guide in the comparable graphs for the arthritic patients.

Perhaps more convincing evidence of deficiency than that shown by the initially low vitamin C values in the cases of rheumatoid arthritis

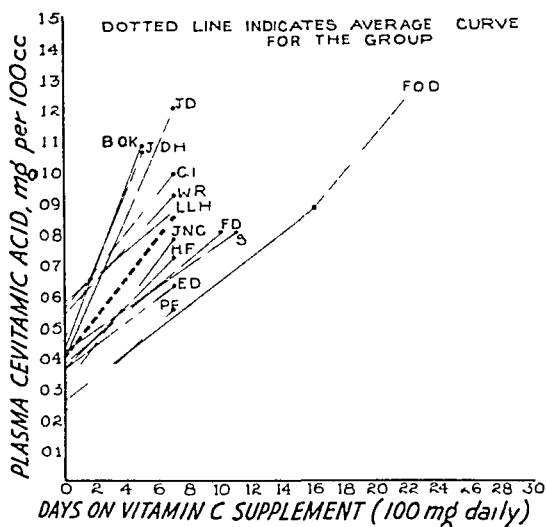


Chart 3—The response of the blood plasma to the administration of vitamin C. These 13 controls showed initial low levels.

is found in a study of the responses to supplementary feeding of vitamin C. Charts 4 and 5 illustrate changes in blood levels following the administration of extra supplements of vitamin C (either as orange juice or as cevitic acid). Data for all cases in which enough determinations were available for graphic representation are shown. The daily supplement was 100 mg or more of cevitic acid. Supplements other than this are indicated in individual curves. No restriction was placed on the diet, in fact, no other instruction was made regarding the dietary intake. In a number of instances a moderately generous intake of vitamin C was included in the patient's usual diet. It will be seen that a considerable amount of extra vitamin C was required to bring the blood level within a normal range. In the cases of rheu-

matoid arthritis (chart 4) an average of somewhat more than 2 Gm of extra vitamin C supplement was needed to bring the vitamin C level up to the lower limits of normal (leaving out of consideration the patients who failed to show a significant rise) This value is in the

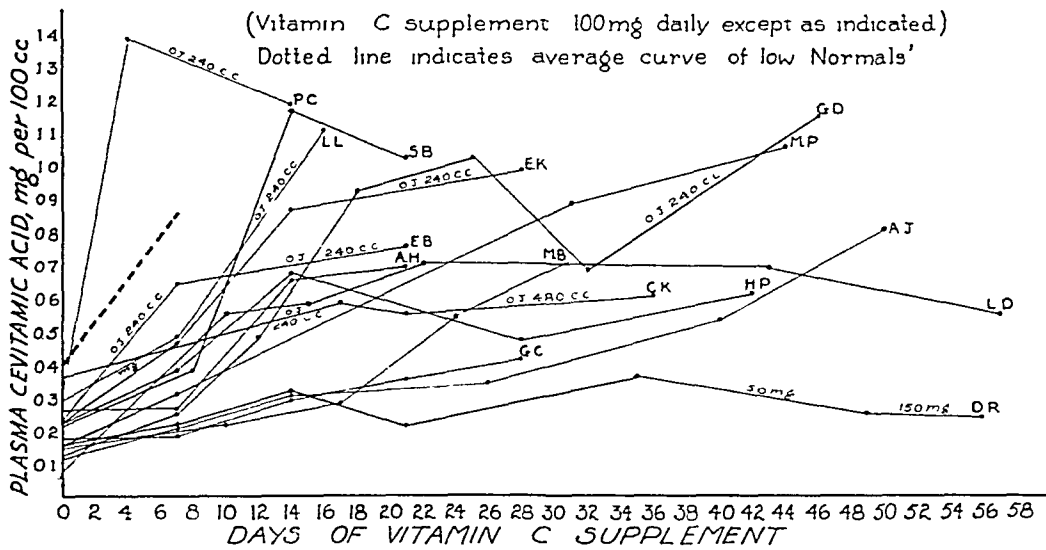


Chart 4—The response of the blood plasma to the administration of a daily supplement of vitamin C in cases of rheumatoid arthritis *O J* indicates orange juice

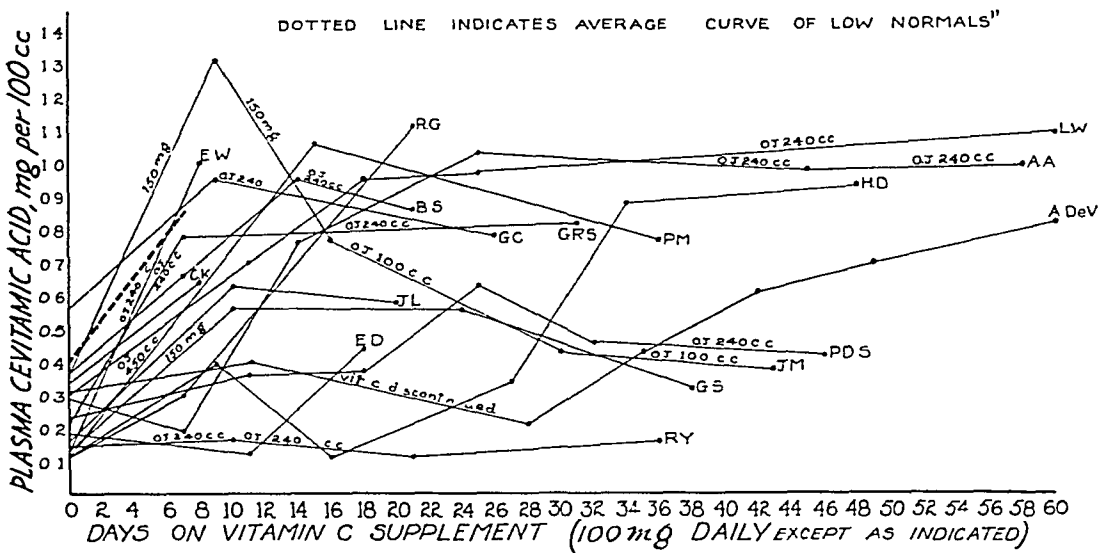


Chart 5—The response of the blood plasma to the administration of vitamin C in cases of arthritis of the rheumatoid type

range of that required to saturate a deliberately depleted person¹⁰ In the cases of rheumatoid arthritis there was on the average, a delay

10 O'Hara, P and Hauck H M Storage of Vitamin C by Normal Adults Following a Period of Low Intake, *J Nutrition* 12 413, 1936

of one week before any significant elevation of the plasma occurred. In certain cases there was a remarkably delayed response. Similar but somewhat less refractory responses were noted in the cases of arthritis of the rheumatoid type (chart 5). In several instances in both groups there was no significant plasma response after prolonged controlled dietary supplements. The precise metabolic fault in these cases has not been determined. One of the most refractory cases was that of D. R. (chart 4). Although a controlled vitamin C supplement was maintained in this case much longer than the fifty-eight days shown in the graph, no significant rise in the plasma level occurred. That the fault in this instance was probably not one of absorption is indicated by a recent determination of the urinary excretion of vitamin C. In the twenty-four hour period of observation, 44 mg. of vitamin C was excreted, although during fasting the blood level was only 0.11 mg. per hundred cubic centimeters. Such cases require more careful study. A lowered renal threshold is a possible mechanism. This person is one of a number whom we have observed who apparently had a basic fault in vitamin C metabolism. Such persons often give a history of a moderate or generous intake of vitamin C in their diet but in spite of this they show depressed vitamin C levels and persistent smouldering arthritic activity. It appears then that deficiency of vitamin C may exist in the presence of an adequate intake.

GONORRHEAL ARTHRITIS

Gonorrhea could be reasonably established in the etiologic background of only 13 persons. It is possible that in some of the cases of arthritis of the "rheumatoid type," gonorrhea had been contributory. Initial vitamin C values for the patients with gonorrheal arthritis were, in general, low, ranging from 0.09 to 0.64 mg. per hundred cubic centimeters and averaging 0.22 mg. The majority of the patients were not febrile or severely ill at the time of examination. It is interesting to speculate on the significance of this finding. That infection may serve to deplete the organic reserve of vitamin C is well supported by considerable evidence.¹¹ Another interpretation that naturally suggests itself is that arthritis develops because of a lowered resistance of the articular tissues to bacterial localization secondary to mild or moderate vitamin C deficiency. That the deficiency is in most instances somewhat milder in these cases is indicated by the relatively prompt rise of the vitamin C level with a supplemented intake (chart 6). That

11 (a) Faulkner, J. M., and Taylor, F. H. L. *Vitamin C and Infection*, J. Clin. Investigation **15** 472, 1936. (b) Perla, David, and Marmorston, Jessie. *Role of Vitamin C in Resistance*, Arch. Path. **23** 543 (April) 1937.

one of the patients (C L) whose data are given in chart 6 was suffering from scurvy seems beyond reasonable doubt. The dietary history indicated a low intake of vitamin C, and the capillary strength was reduced. The gums were reddened and edematous and bled easily.

THERAPEUTIC RESULTS

Our data for judgment of the therapeutic value of a high intake of vitamin C in arthritis we do not believe are adequate for statistical analysis, but clearcut clinical improvement has occurred in the majority of cases. The only other form of treatment in our cases has been selective physical therapy. It is interesting that in the majority of instances of recurrence we have found the cevitic acid content of the plasma

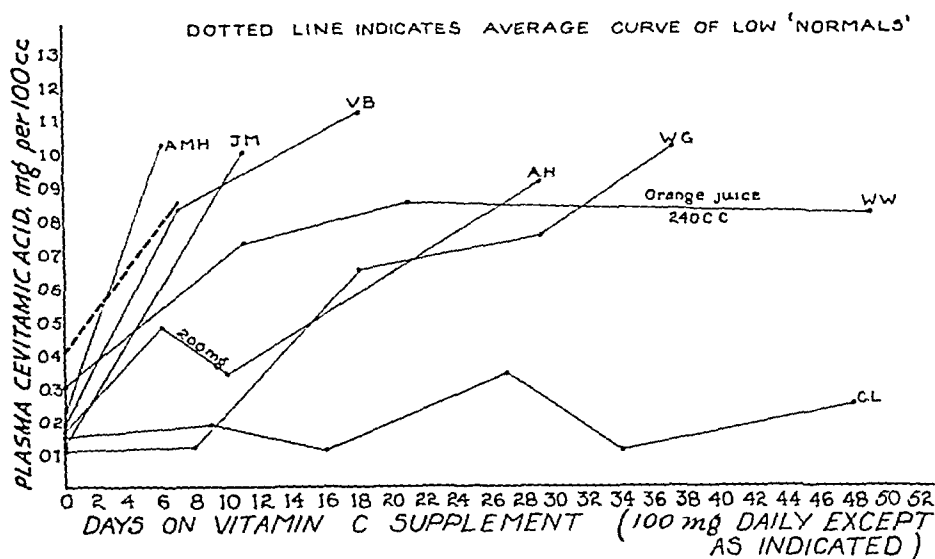


Chart 6—The response of the blood plasma to the administration of vitamin C in cases of gonorrheal arthritis

depressed. The most satisfactory clinical responses occurred in the cases in which there was a satisfactory rise of the cevitic acid content. The results in the few cases in which daily intravenous administration of the sodium salt of cevitic acid was combined with supplements of vitamin C by mouth have been particularly encouraging.

COMMENT

As has been pointed out, it is obvious that the vitamin C content of the plasma is an index only of the immediate nutritive status of the individual relative to this food factor. However, the practically uniform finding of low vitamin C values in a large series of cases of rheumatoid arthritis must be significant. Sherwood¹² has briefly

¹² Sherwood K. K. Clinical Significance of Vitamin C, Kings Co Hosp Bull 4 7 1937

recorded similar observations, and Peila^{11b} has cited unpublished data of Finkle that appear corroborative. Except in a few instances, we do not believe that our patients were suffering from degrees of infection that would cause vitamin C depletion. In fact, the majority were afebrile, and in many no infection could be demonstrated. We do not deny the influence of infection, which has been emphasized particularly by Cecil¹³. However, we do not believe that infection alone is responsible for the disease. In some cases a chronic lack of vitamin C may prepare the articular tissues for localization of bacteria of low virulence. Convincing evidence of deficiency is indicated in the curves showing delayed saturation following the giving of a supplement. The data here recorded are considered as conclusive as such data can be and to afford strong support for the thesis that chronic vitamin C deficiency is of major etiologic significance in many cases of rheumatoid arthritis or polyarthritis of the rheumatoid type. If subacute or chronic vitamin C deficiency produces comparable arthritis in experimental animals, it is not unreasonable to believe that it may do so in man.

SUMMARY AND CONCLUSIONS

The cevitamic acid level of the blood plasma during fasting is almost uniformly and severely lowered in rheumatoid and rheumatoid types of arthritis. In the majority of cases the blood level rises after the administration of vitamin C. Usually this rise is delayed. These data indicate the existence of vitamin C deficiency in arthritis of this type, and we believe they afford significant support for the thesis that chronic deficiency of vitamin C is an important factor in the etiology of the disease. Some patients appear to present a fundamental fault in vitamin C metabolism. The plasma levels during fasting fail to rise after prolonged administration of generous supplements of vitamin C, although the urinary excretion may be relatively high. A lowered renal threshold is a possible mechanism. Low vitamin C levels are the rule in gonorrheal arthritis. It is suggested that deficiency of vitamin C predisposes to bacterial localization in this group and possibly also in the other groups. In the small series of cases of hypertrophic arthritis the plasma values were almost uniformly high. Apparently deficiency of vitamin C may exist in the presence of an ordinarily adequate dietary intake. Our preliminary therapeutic observations have been distinctly encouraging. Such studies to be conclusive should be rigidly controlled and should be extended over an adequate period.

13 Cecil, R. L. Rheumatoid Arthritis, *J. A. M. A.* **100** 1220 (April 22) 1933

DISCUSSION

DR M P SCHULTZ, Washington, D C Since Dr Rinehart and his colleagues made the brilliant observation that in guinea pigs subject to the combined influence of chronic scurvy and infection with group C hemolytic streptococci a characteristic form of nonpurulent carditis develops, these experiments have been repeated, as has just been stated, by four groups of investigators. The findings of Dr Rinehart have been confirmed, in that cardiac damage of the type he originally described develops in guinea pigs subjected to chronic scurvy plus infection or, as appears to be indicated by recent work, uncomplicated acute scurvy. It should be pointed out, however, that none of the subsequent observers considers that these lesions bear a close resemblance to those of rheumatic fever.

From the clinical standpoint, as Dr Rinehart has mentioned, the subject has received the attention of several investigators. Warner, Winterton and Clark in a dietary study found that rheumatic children consume as much or more food containing vitamin C than do controls. They stated, indeed, that on the basis of their study the relation between rheumatic fever and scurvy suggested by Dr Rinehart cannot be supported. The experiments of Perry and his co-workers, in which the degree of vitamin C saturation of patients with rheumatic fever and of controls was studied, also did not support this hypothesis.

Dr Rinehart has described in part the experiments of this type which were undertaken at the Hospital of the Rockefeller Institute—work with which I was associated. Because evidence of C hypovitaminosis was by no means found to be regularly associated with rheumatic fever, because similar degrees of deficiency were found to be present in other disease states and because treatment with large doses of the vitamin were ineffective, we concluded that scurvy is not an important factor in the pathogenesis of rheumatic fever. We considered that those experiments in which subjects received 100 mg of cevitamic acid daily in addition to their habitual diet (which in many instances did not seem to be inadequate) for several months before rheumatic fever developed in severe and typical form were of especial significance. These patients received several times the quantity of the vitamin considered sufficient to prevent the development of scurvy, and when their degree of saturation with cevitamic acid was tested after the development of rheumatic fever, no severe degree of C hypovitaminosis was found to be present.

The work of Abassy, Hill and Harris has been described at some length by Dr Rinehart as in support of his conclusions. These observers found an apparent degree of scurvy in most but not all patients with acute or chronic rheumatic fever. The findings in this group differed little from those for patients with active or semiactive tuberculosis. In patients with quiescent tuberculosis, on the other hand, and in controls a comparable degree of hypovitaminosis was not present. These authors pointed out, indeed, that in cases of active infection, either rheumatic or tuberculous, there is frequently a deficit with respect to this vitamin, whereas in the absence of active infection this is not so likely to occur. They stressed the point that in the group of patients with quiescent tuberculosis, active infection is no longer present—the process has healed. They were emphatic that on the basis of their work it cannot be concluded that in patients with rheumatic fever there is any alteration in vitamin C metabolism which is not present also in patients with other infections.

Investigators in this field are unanimous in the conclusion, so strikingly demonstrated by the extensive work of Dr Rinehart, that degrees of C hypovitaminosis do occur in patients with rheumatic fever. It would indeed be surprising if this were not the case. In the past few years about a dozen studies have been made of

vitamin C metabolism in various infections. The degree of saturation with this vitamin has been investigated by measuring the excretion after test doses or by estimating the cevitamic acid content of the blood of patients with various infections, for instance, tuberculosis, pneumonia, typhoid fever, furunculosis and sepsis. Studies of this character have demonstrated a tendency to C hypovitaminosis in all the infectious states which have been investigated. Two of these papers are especially pertinent, Widenbauer determined the daily dose of vitamin C necessary to maintain excretion at an optimum level and compared variations in the quantity requisite with alterations in the erythrocyte sedimentation rate. There was a striking parallel, with increased severity of the infection, as indicated by an accelerated sedimentation rate, there was an increase in the amount of vitamin necessary to maintain the balance. This author, familiar with the work of Dr Rinehart, included cases of rheumatic fever in the series. The behavior of these patients differed in no way from that of patients with other types of infection, chiefly tuberculosis. Graphs were presented demonstrating that a patient in balance with respect to vitamin C with a certain daily dose requires a greatly increased quantity immediately on the development of a dental abscess, but his requirement returns to the former level when the abscess is drained. A few days later a corresponding rise and fall of the sedimentation rate takes place. This parallel between the amount of cevitamic acid required and the sedimentation rate was regularly demonstrable.

The other investigation which seems particularly pertinent to the present discussion was carried out by Baer, who observed the degree of vitamin C subnutrition by means of saturation tests of 35 patients with acute pharyngitis. Hypovitaminosis with respect to vitamin C was so regularly found and was of such extreme degree that this author suggested that acute pharyngitis may be one manifestation of this deficiency condition. The 35 patients studied represented a wide range of ages, and although the local infection of the throat was in many cases severe and the degree of scurvy in each instance was definite, neither rheumatoid arthritis nor rheumatic fever developed as a complication.

Concerning the careful and extensive study which Dr Rinehart has described, only two questions occur. The first is regarding the method of titration used. The determination of reduced cevitamic acid by the method of Farmer and Abt possesses certain advantages, in that it is easily and rapidly performed and requires a minimum of chemical manipulation. The disadvantage lies in the fact that reduced cevitamic acid is readily converted to the reversibly oxidized form—a slight degree of hemolysis in the serum, for instance, accelerates this change and may be responsible for false low readings. As reported in the *Proceedings of the Society for Experimental Biology and Medicine*, Dr Piojan, of Rochester, N. Y., attempting to use the method as originally described by Farmer and Abt (presumably the unmodified method which Dr Rinehart employed) found it entirely unreliable. Further investigation demonstrated that false low readings were obtained unless the specimens were titrated immediately after the blood was drawn. Dr Piojan emphasized the fact that no more than thirty minutes should elapse between the drawing of blood and the titration if reliable data are to be obtained. Since Farmer and Abt did not mention the necessity of observing this precaution and in view of the extremely low values which Dr Rinehart reports, the observations of Dr Piojan appear to be pertinent. I wish to inquire therefore, if in the experiments just reported all titrations were performed within the recommended time limit.

The other question is with regard to medication received by the patients. Daniels and his colleagues have reported from Iowa that the administration of

acetylsalicylic acid to febrile children results in increased excretion of vitamin C. These authors suggested that the unusually low figures which Dr Rinehart reported for children may be the result of depletion of vitamin C reserves by antecedent medication with acetylsalicylic acid. I am aware that Youmans and his colleagues have since reported that in afebrile adults this effect of acetylsalicylic acid could not be demonstrated. Since patients with rheumatic fever are usually febrile children, however, conclusions concerning vitamin C metabolism must be regarded with reservation if the subjects studied had received acetylsalicylic acid or other salicylates. In view of the difficulty in finding arthritic patients, especially those with rheumatic fever, who have not been treated with these drugs, I wish to inquire if Dr Rinehart eliminated this complicating factor in the present study.

Dr Rinehart and his colleagues have made a valuable extensive study of vitamin C metabolism in infection. In the light of all information at present available on this subject, however, it would be unjustifiable to conclude that the disturbances in rheumatic fever are of greater significance than those of similar character observed in other infections.

DR A. ALMON FLETCHER, Toronto, Canada. It is not easy to assess the significance of Dr Rinehart's observations. It is reasonable to propose that behind the development of rheumatic disease there is some chronic nutritional disorder. It is not likely that the answer to this important question will be found in the administration of a few tumblerfuls of orange juice or by the analysis of the patient's diet, because chronic nutritional disorders are likely to be, to a large extent, irreversible or slowly modified by dietetic treatment.

The production in experimental animals by means of vitamin C deficiency of lesions comparable to those of rheumatic fever and rheumatoid arthritis is suggestive but does not by any means prove that these lesions are identical with those occurring in man. It is difficult to believe that many patients with rheumatoid arthritis are suffering from subclinical scurvy. Occasionally the spongy, bleeding gums referred to by Dr Rinehart are seen, and they undergo prompt improvement with the administration of vitamin C. Much more frequently such changes are absent, and at times patients with rheumatoid arthritis are made worse by the administration of large amounts of fruit.

There is much clinical experience to suggest that patients with rheumatoid arthritis are helped by high vitamin diets, and at times the liberal administration of vitamin C appears to be of value. Such measures suggest that if chronic disturbed nutrition contributes to the development of this disease, the disturbance is of a nonspecific character in which vitamin C may at times be one factor.

DR JAMES M. FAULKNER, Boston. I find myself in such close agreement with Dr Schultz' remarks that I have little to add. The question seems to be essentially whether the low cevitic acid values for the blood which Dr Rinehart finds in patients with rheumatic fever are a cause or an effect. Now, it has been recognized ever since the publication of the earliest observations on scurvy, three hundred and fifty years ago, that infection is an important predisposing cause of scurvy. Dr Rinehart has just demonstrated that the blood level of cevitic acid is usually reduced not only in rheumatic fever but in other infectious diseases the etiology of which is well established. My colleagues and I have had the opportunity at the Boston City Hospital of estimating the blood values for cevitic acid for patients with and without infection. All these patients had been receiving diets generally considered adequate as to the vitamin C content. For 43 subjects without infection the average cevitic acid value was 131 mg per hundred cubic centimeters, while for 66 patients suffering from miscellaneous

infectious diseases the average value was 0.64 mg. Among the patients with infection there were 10 with acute rheumatic fever for whom the average value was 0.48 mg. We did not regard the slight difference in average value for the patients with rheumatism and those with miscellaneous infections as significant. We also had the opportunity to study the vitamin C balance of a patient with active pulmonary tuberculosis. The patient was maintained on a diet almost completely lacking in vitamin C and was given measured amounts of pure cevitic acid. It was found that it took 300 mg. of cevitic acid daily by mouth to bring the blood level and urinary excretion of this substance to normal. Similar observations in a case of acute rheumatic fever revealed the same increased requirement, namely 300 mg. per day.

It seems to me that Dr. Rinehart's observations might be explained on the basis of a nonspecific effect of infection on the metabolism of vitamin C analogous to the effect of infection on the metabolism of iron or of vitamin B. If vitamin C undernutrition were an important etiologic factor in rheumatic fever one would expect to see rheumatic fever occasionally in the presence of clinical scurvy. I have not yet seen this combination.

DR. RUSSELL L. CECIL, New York. Dr. Rinehart was kind enough to send me some of his sections last winter, and I was greatly interested in some of the lesions produced in the guinea pig. It seemed to me that while there were some lesions that showed an infiltrative reaction, the infiltration was not as active as is seen in typical rheumatic fever. I should think that controls with other vitamins would be important in this connection. The fact that the patient fails to improve when fed on vitamins is disappointing. The question after all is this: Is this deficiency in vitamin C the cause or the effect of the disease?

DR. JAMES F. RINEHART, San Francisco. Dr. Schultz has raised a number of questions that are difficult to answer. The data presented here are not considered a final answer to the problem, but I believe they indicate an imperative need for adequately controlled prophylactic and therapeutic studies. The bulk of the evidence available at present indicates that the reduced form of cevitic acid is the significant and physiologic active form of the vitamin. Dr. Schultz has cited the excellent work of Warren, Winterton and Clark. This study is particularly painstaking, but I do not believe that it is conclusive. A gross estimate of the intake of fruits and vegetables does not give an accurate idea of the vitamin C intake, because of the varied content of this factor in different foods. With respect to the reliability of the methods used, I may say that my colleagues and I have investigated particularly carefully all possible pitfalls in the methods, and the evidence, which we cannot go into at this time, we believe indicates that they are entirely reliable. Data pertaining to the possible influence of acetylsalicylic acid on the excretion of vitamin C are controversial. As far as we know, there is no effect of this drug on the blood level, also many of our patients were not receiving any form of salicylates. We have been aware of Dr. Plojan's criticism of the method and can say without hesitation that it is not valid.

I wish to thank Dr. Fletcher for his conservative discussion of this paper and to reemphasize what has been said. Indeed, the answer to the problem will not be found by giving a few glasses of orange juice to the patients.

Dr. Faulkner has raised a pertinent question, that is, whether the low levels of vitamin C in the blood plasma are not secondary to the disease. This question perhaps particularly applies to acute rheumatic fever. There is every indication that infection itself serves, at least in some degree, to deplete the vitamin C reserve. We believe it to be particularly significant that approximately 75 per cent of the patients with

chronic or inactive rheumatic fever have a significantly low vitamin C level of the plasma. This is in agreement with the work of Abbasy, Harris and Hill. An inactive disease would hardly deplete the vitamin C reserve. There is no reason to believe that the levels recorded do not represent habitual values for these subjects. In patients with rheumatoid arthritis, particularly, only occasionally have we seen severe infection preceding the onset of the disease, and in the patients in whom we have been able to demonstrate focal infection the latter has not been of a degree that might deplete the vitamin C reserve. Most of the patients included in this study were in the outpatient department and were ambulatory and except for the arthritic disability showed no striking manifestations of infection. Obviously, and in our experience, not only are low vitamin C levels of the blood found for patients with rheumatic fever and rheumatoid arthritis, but they have been practically consistently found for patients with these diseases. This consistency makes the finding significant. The question has been raised again why we do not see rheumatic fever in patients with scurvy. I do not believe that any one has sufficient data to answer this question. Obvious scurvy is a late and severe form of vitamin C deficiency. Clinically manifest scurvy is seen practically only in infants and adults. It is uncommon to find recognizable scurvy in a person of the rheumatic fever age group. Is it not possible that this unrecognized scurvy is present in rheumatic fever or rheumatoid arthritis? If a disease resembling rheumatic fever or rheumatoid arthritis can be produced in animals by vitamin C deficiency, it is entirely reasonable that the same deficiency would produce comparable states in human beings. The evidence of this and other studies indicates that significant degrees of vitamin C deficiency exist rather commonly, particularly among poorer persons. Where then are the diseases that result from this? Dr Cecil has asked why patients fail to improve with an increased intake of vitamin C. An adequate study of the effect of a high intake of vitamin C in these diseases has not yet been made. In some cases the requirement is abnormally high. As Dr Fletcher has said, the administration of a few glasses of orange juice will not answer the problem. A high intake of vitamin C, controlled by chemical studies of the blood, must be maintained over a long period, and patients must be followed with care for adequate evaluation. Certain of the deformities produced will not be corrected by any method.

In summary, I may say that not only experimental but clinical, epidemiologic and biochemical studies all point to the possible importance of vitamin C deficiency in the etiology of rheumatic fever and rheumatoid arthritis. These data indicate clearly the importance of comprehensive preventive and therapeutic studies. Adequate control and long periods of observation are necessary.

METABOLISM OF VITAMIN C IN RHEUMATIC FEVER

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Since the suggestion was originally made that vitamin C deficiency may be an important factor in the etiology of rheumatic fever,¹ there has been considerable study of this problem. The concept was based on experimental observations that a pathologic state with certain similarities to rheumatic fever may be produced by subjecting guinea pigs to the simultaneous influence of vitamin C deficiency and streptococcal infection. The reports recorded the occurrence of lesions comparable to those of rheumatic fever in the cardiac valves, cardiac muscle and joints of the experimental animals so treated. The well known epidemiologic peculiarities of rheumatic fever, notably the geographic, seasonal and social incidence, are in accord with such a concept. A conditioning environmental influence is suggested particularly by the dominant occurrence of the disease in the poor.

Stimson, Hedley and Rose² soon offered confirmation of the experimental work and added a brief report on the production of a degenerative and proliferative myocardial lesion bearing some resemblance

Read before the American Rheumatism Association, Atlantic City, N J, June 7, 1937

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This investigation was supported by the Christine Breon Fund for Medical Research and by the California Fruit Growers' Exchange. Hoffmann-LaRoche, Inc., furnished supplies of vitamin C.

1 Rinehart, J F, and Mettier, S R. The Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection, with Notes on the Similarity of the Lesions to Those of Rheumatic Fever, *Am J Path* **10** 61, 1934. Rinehart, J F, Connor, C L, and Mettier, S R. Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, *J Exper Med* **59** 97, 1934.

2 Stimson, A M, Hedley, O F, and Rose, E. Notes on Experimental Rheumatic Fever, *Pub Health Rep* **49** 361, 1934.

to the Aschoff reaction induced by intracardial injection of streptococcus toxin in scorbutic guinea pigs. They suggested that the ability of an organism to produce such lesions might, in part, be dependent on its production of toxin. Schultz³ likewise produced nonpurulent carditis by means of the synergistic influence of chronic scurvy and hemolytic streptococcal infection. He said he considered that the changes only slightly resembled those seen in rheumatic fever. More recently McBroom, Sunderland, Mote and Jones,⁴ as well as Taylor,⁵ have recorded the occurrence of degenerative and proliferative reactions in the cardiac valves of scorbutic animals in which a factor of infection was not experimentally introduced. They observed no clear difference in their animals in which experimental infection was superimposed on the scorbutic state. It is of significance that for the most part the streptococci used by these authors were derived from human sources and were not satisfactory infecting agents for guinea pigs.⁶ In our original work, streptococci derived from guinea pigs and natural pathogens for guinea pigs were used. In our own experience the virulence of the infecting organism is important in the production of the "rheumatic-like" pathologic picture. Furthermore, we believe that some of the lesions produced by us are more like those of rheumatic fever than those described by the authors cited. Taylor recorded the finding of small numbers of bacteria in the cardiac muscle of scorbutic animals not experimentally infected.

All agree that infection alone, in the presence of an adequate diet, does not produce rheumatic-like lesions. Recently several clinical approaches to the problem have been made. Warner, Winterton and

3 Schultz, Mark P. Cardiovascular and Arthritic Lesions in Guinea-Pigs with Chronic Scurvy and Hemolytic Streptococcal Infections, *Arch Path* **21** 472 (April) 1936

4 McBroom, Josephine, Sunderland, Douglas A., Mote, John R., and Jones, T. Duckett. Effect of Acute Scurvy on the Guinea-Pig Heart, *Arch Path* **23** 20 (Jan) 1937

5 Taylor, S. Scurvy and Carditis, *Lancet* **1** 973, 1937

6 The observations made on the animals in group 5 of Taylor's series are of particular interest. The four pigs used in that experiment received a basal diet free from vitamin C for four weeks. Hemolytic streptococci (human source) were injected intracutaneously, and thenceforth the pigs received 4 cc of orange juice per day. All recovered from the scurvy and gained weight continuously for the remaining fifteen weeks of the experiment. They were then killed. "None showed signs of scurvy post mortem. The livers were very fatty and hearts were all slightly enlarged." The mitral valves were all nodular. Histologically the hearts showed perivascular infiltration, edema and proliferative mitral valvulitis. There was massive endothelial cell infiltration of the auricle in one animal. These observations are potentially of considerable significance, and the study should be repeated with a larger series of animals.

Clark,⁷ in a detailed dietary survey, found the gross consumption of fresh fruits and vegetables by rheumatic persons to be equal to or greater than that by controls. However, at Christ's Hospital an increase in consumption of fruits and vegetables was associated with a fall in the incidence of rheumatic fever. Other dietary changes, however, were made in the same period, notably an increase in consumption of fat (including butter) and of protein. Although this study was remarkably detailed and exhaustive, it is naturally inconclusive. No accurate index of the consumption of vitamin C is possible from a gross estimate of the intake of fresh fruits and vegetables because of extreme variations in the vitamin C content of foods of this sort. Furthermore, inherent or acquired metabolic faults and depleting mechanisms were not considered.

Faulkner⁸ has studied the reticulocyte response in certain chronic infections following administration of generous supplements of vitamin C. A rise of 2 to 4 per cent in the reticulocyte count (young red blood cells) occurred after liberal administration of vitamin C in most cases. This study concerned twenty-seven patients with rheumatic fever, eight with tuberculosis of the bone and two with Still's disease. To us this suggests a reaction following correction of a deficiency.

Perry⁹ examined the vitamin C reserve of five patients with active rheumatic fever and six with quiescent rheumatic fever. His study was based on the urinary excretion following test doses of vitamin C. Although these examinations revealed evidence of deficiency in a number of cases, he concluded that "vitamin C-deficiency is not an important factor in the cause of acute rheumatism," although "mild degrees of this deficiency are not uncommon in rheumatic children." Sendroy and Schultz¹⁰ undertook a careful study of the utilization of vitamin C in rheumatic fever. Eight of thirteen patients showed a utilization of the vitamin above the calculated normal. This the authors ascribed to faulty absorption or digestive disturbance. The existence or nonexistence of a deficiency before dietary modification was not studied by them. More recently Abbasy, Hill and Harris,¹¹ in a direct, uncomplicated experiment, have investigated the problem, studying large numbers of patients. Their series included one hundred and seven patients with

7 Warner, Edwin C., Winterton, Frank G., and Clark, M. L. A Dietetic Study of Cases of Juvenile Rheumatic Disease, *Quart J Med* **28** 227, 1935.

8 Faulkner, James. The Effect of Administration of Vitamin C on the Reticulocytes in Certain Infectious Diseases, *New England J Med* **213** 19, 1935.

9 Perry, C. B. Rheumatic Heart Disease and Vitamin C, *Lancet* **2** 426, 1935.

10 Sendroy, Julius, and Schultz, Mark P. Studies of Ascorbic Acid and Rheumatic Fever, *J Clin Investigation* **15** 369, 1936.

11 Abbasy, M. A., Hill, N. Gray, and Harris, Leslie J. Vitamin C and Juvenile Rheumatism, *Lancet* **2** 1413, 1936.

active rheumatic fever, eighty-six convalescent patients, together with sixty-four controls, and forty-two patients with surgical tuberculosis in the earlier stages of the disease, as well as forty-six with quiescent surgical tuberculosis. All the children were hospital patients and had for some time received in their diet more vitamin C than the reputed minimum standard. These authors found a striking decrease in the excretion of vitamin C (evidence of vitamin C deficiency) of the patients with active rheumatic fever, patients convalescing from rheumatic fever and patients with active tuberculosis. Those with quiescent tuberculosis showed a normal excretion. Further, it was found extremely difficult to "saturate" the rheumatic children with vitamin C. In other words, it was found that the rheumatic children were in a lowered state of nutrition relative to vitamin C, and it was concluded that there is a greatly increased metabolic use of (and need for) vitamin C in rheumatic fever. Accordingly the authors recommended the giving of large amounts of the vitamin both therapeutically and prophylactically. The finding of unsaturation in patients with inactive rheumatic fever and those convalescing from rheumatic fever suggests either an unusual depletion or a greater than average requirement for vitamin C in "rheumatic" children.

Farmer and Abt¹² have recently described a method for the determination of the reduced ascorbic acid content of the blood plasma and have reported that the values obtained by this method parallel the intake of vitamin C and are an accurate index of the nutritive state relative to this food. We¹³ have confirmed this work, showing that in normal persons the vitamin C content of the plasma during fasting is an accurate index of the intake of vitamin C and that the data so obtained are comparable to those obtained by studies of urinary excretion. The method affords a simple and direct way of determining the immediate nutritive status of a person relative to vitamin C. If serial determinations are made with a controlled intake of the vitamin, an estimate of the degree of unsaturation can be ascertained. Using this method of study, we¹⁴ reported briefly the almost consistent finding of a low vitamin C content of the plasma in cases of rheumatic fever in which significant modification of the dietary habit had not been made preceding the determination. The present report deals with a more extended study of the problem, similar methods being used. From accumulated evidence

12 Farmer, Chester J., and Abt, Arthur F. Ascorbic Acid Content of Blood, *Proc Soc Exper Biol & Med* **32** 1625, 1935.

13 Greenberg, L. D., Rinehart, J. F., and Phatak, N. M. Studies on Reduced Ascorbic Acid Content of the Blood Plasma, *Proc Soc Exper Biol & Med* **35** 135, 1936.

14 Rinehart, J. F., Greenberg, L. D., and Christie, A. U. Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever, *Proc Soc Exper Biol & Med* **35** 350, 1936.

we believe that optimal levels of the vitamin C content of the blood for children are above or at 0.9 mg per hundred cubic centimeters. Values between 0.7 and 0.9 mg are probably adequate, but values below 0.5 mg must be considered low.

The present report is based on a study of forty-two patients with active rheumatic fever and twenty-two with "interval" rheumatic fever without clinical evidence of activity. The great majority of the patients were children. One control group consisted of nineteen children admitted to the University of California Hospital for tonsillectomy. These

TABLE 1—Vitamin C Content of the Blood

	Vitamin C, Mg per 100 Cc			Values Below 0.5 Mg, %
	No. of Cases	Range	Average	
Acute rheumatic fever, unmodified diet	30	0.11-0.63	0.30	97
Acute rheumatic fever, modified diet*	12	0.12-0.83	0.57	25
Inactive rheumatic heart disease (adults and children)	22	0.10-1.20	0.38	78
Miscellaneous infections (children)	92	0.08-1.29	0.48	59
Miscellaneous noninfectious pathologic states (children)	67	0.13-1.50	0.76	28
Controls (tonsillectomy and adenoidectomy)	19	0.22-1.57	0.81	26
Tuberculosis (hospitalized children)	110	0.09-1.53	0.79	25
Tuberculosis (newly admitted children)	6	0.11-1.21	0.81	33

* The individual plasma level and the dietary modification in each case were as follows:

Patient	Cevitamic Acid, Mg per 100 Cc	Diet Modification
J. P.	0.83	Approximately 3 liters of orange juice during 4 days prior to analysis
W. B.	0.62	500 cc. of tomato juice daily for past 3 weeks
W.	0.82	Approximately 1 liter of orange juice daily for 2 wk. prior to analysis
B. B.	0.74	Considerable increase in vitamin C intake during past month
M. W.	0.71	Orange juice, 750 cc. daily for 5 days prior to analysis
F. W.	0.18	Approximately 1 liter of orange juice daily for 1 wk. prior to analysis
G. B.	0.12	One month ago, 1 liter of tomato juice for about 2 weeks, then orange juice, 1 liter up to 1 week ago
O. N.	0.48	Orange juice or tomato juice, 250 cc. daily for past month
J. M.	0.50	Orange juice, approximately 200 cc. daily during past 5 months
B.	0.65	Orange juice, 2,500 cc. during 2½ days preceding test
P. K.	0.61	Increased vitamin C intake for past 3 weeks (since onset of present illness)
J. C.	0.57	High vitamin C diet for past 4 days

children were of the same social status as those with rheumatic fever. Other control groups include ninety-two children with miscellaneous infections and sixty-seven patients with miscellaneous pathologic conditions unassociated with obvious infection (table 1). With few exceptions all determinations were made on blood samples taken with the subject in the fasting or postabsorptial state.

The patients with active rheumatic fever included thirty patients for whom no significant modification of the diet was known to have been made prior to the initial analysis. Twelve patients must be considered separately because a rather marked increase in the intake of vitamin C was instituted prior to the first plasma determination. A summary of the data relative to the several groups is given in table 1. It is seen that the vitamin C content of the blood was almost uniformly

lowered for patients with active rheumatic fever whose diet had not been significantly changed preceding the test. The average value for this group was 0.3 mg per hundred cubic centimeters, 97 per cent showed values below 0.5 mg, which is considered the lower limit of "normal." These values lie in the range which Ingalls¹⁵ said he considered indicates definite deficiency. This study adds support to the idea that infection per se acts to deplete the vitamin C reserve. However, the patients with nonrheumatic infection were not found to be depleted as uniformly or as strikingly as those with rheumatic fever, although in most instances the clinical evidence of active infection was more prominent.

A large group of tuberculous children who had been hospitalized for a few days to several years were available for study. Because they had been hospitalized and had received moderate or generous supplements of vitamin C, they were not entirely suitable as controls. However, the discovery that approximately 50 per cent of them showed a vitamin C value at or above 0.9 mg per hundred cubic centimeters suggests that this is probably the optimal metabolic range for children. Of particular interest is the group of patients with chronic or inactive rheumatism. The average level for the twenty-two patients was 0.39 mg. Seventy-six per cent gave values below 0.5 mg. A subdivision of this group is of even greater interest. Eight rheumatic children, whom we had been following in the clinic for six months to three years, were examined during the spring of 1937. They showed no clinical evidence of an active rheumatic process. The respective vitamin C levels of the plasma were as follows: 0.18, 0.18, 0.14, 0.18, 0.1, 1.2, 0.45 and 0.24 mg per hundred cubic centimeters. Only one of the entire group showed a satisfactory plasma value, and six of the eight showed values which were in the lowest ranges. This is the more remarkable in that these patients had been repeatedly urged to include liberal amounts of vitamin C in their diet. These data show that a high percentage of "rheumatic" patients, though not suffering from active disease, are in a potential if not an actual scorbutic state. It is obvious that any therapeutic study directed at estimation of the protective value of vitamin C against the onset or recurrence of rheumatic fever must be rigidly controlled.

It was possible to make one or more determinations of the vitamin C content of the plasma for nineteen of the patients with active rheumatic fever after the administration of liberal supplements of vitamin C. The results are shown graphically in chart 1. It will be seen that there are three general types of curves. Eight patients showed a relatively

¹⁵ Ingalls, T. H. Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, *J. Pediat.* **10**: 577, 1937.

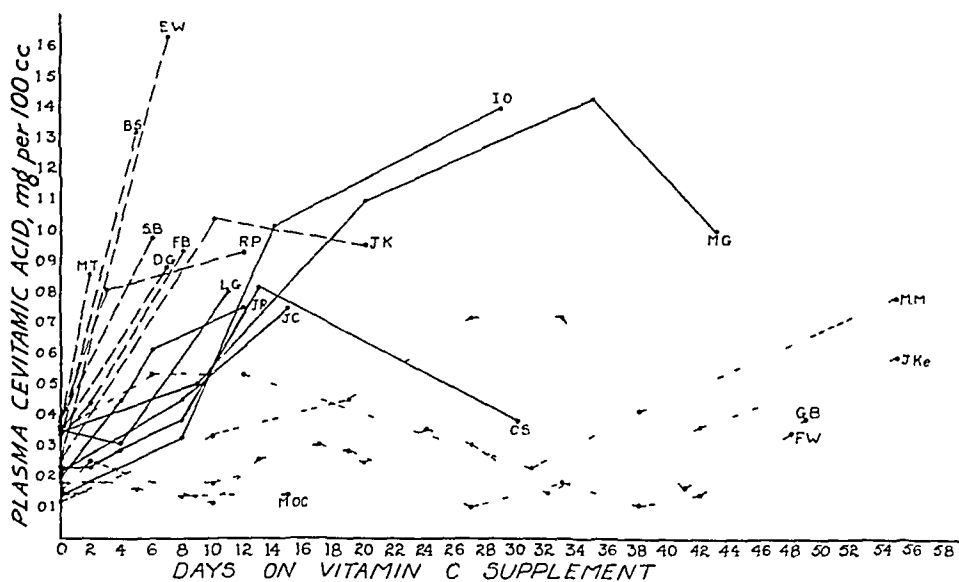


Chart 1—Metabolism of vitamin C in rheumatic fever. Curves for patients with active rheumatic fever, showing the response of the blood plasma to the administration of vitamin C.

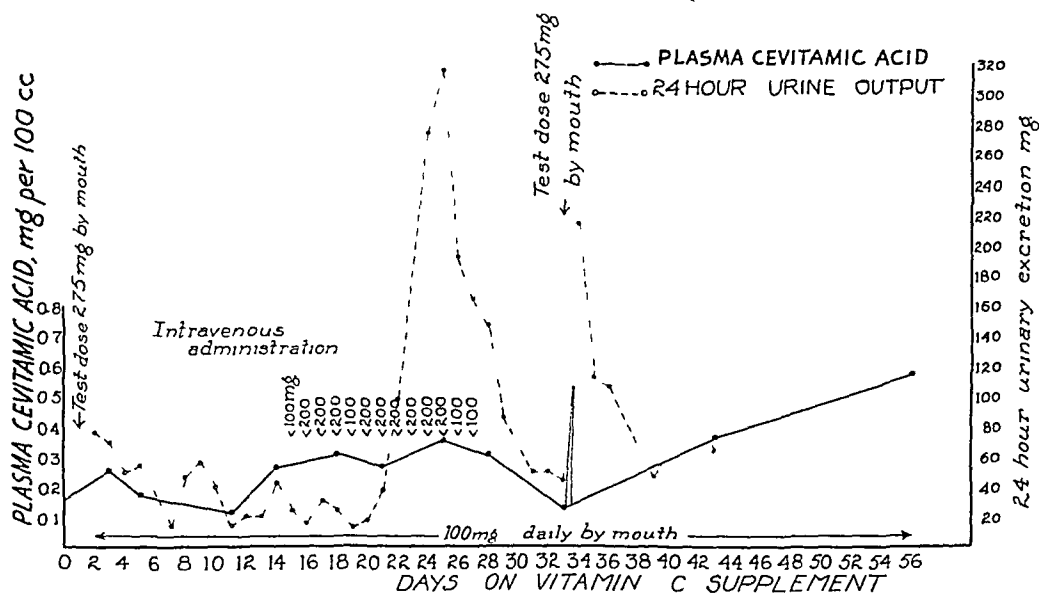


Chart 2—Metabolism of vitamin C in rheumatic fever. Parallel curves of the cevitamic acid content of the plasma and of the twenty-four hour urinary excretion of cevitamic acid, illustrating the abnormal metabolism in a case of rheumatic fever.

prompt rise in the plasma value, six exhibited a rise but with a decided lag. Five exhibited an unexpected and as yet unexplained phenomenon in that they failed to show a satisfactory response even after prolonged and massive doses of the vitamin. One such case is of great interest.

J. Ke, a 15 year old boy, had the initial rheumatic injury of the heart six years before the present study was made. He entered the hospital with recurrent acute rheumatic fever associated with severe decompensation. In this instance we had the opportunity to make repeated estimations of the vitamin C content

TABLE 2—Daily Vitamin C Supplement in Cases Illustrated in Chart 1

Patient	Age, Years	Treatment, Days	Daily Supplement of Vitamin C
M. T.	9	2	Orange juice, 250 cc
B. S.	8	5	Vitamin C, 100 mg
E. W.	9	7	Orange juice, 500 cc
R. P.	14	12	Orange juice, 500 cc
D. G.	5	7	Vitamin C, 100 mg
F. B.	11	7	Orange juice, 500 cc
J. H.	6	2	Vitamin C, 200 mg
		3-20	Vitamin C, 150 mg
S. B.	5	6	Vitamin C, 100 mg
I. R.	13	12	Vitamin C, 150 mg
M. G.	13	44	Orange juice, 500 cc
L. G.	8	11	Orange juice, 500 cc
J. C.	8	15	Orange juice, 500 cc
I. O.	13	29	Vitamin C, 100 mg
C. S.	22	0	Vitamin C, 550 mg (test dose)
		2	Vitamin C, 550 mg (test dose)
		3	Vitamin C, 50 mg
		4-7	Vitamin C, 100 mg
		8-13	Vitamin C, 200 mg
		13-30	At home, intake uncertain
G. B.	21	14	Vitamin C, 200 mg, and orange juice, 500 cc
		15-18	?
		19-49	Vitamin C, 200-250 mg
M. M.	11	55	Orange juice, 500 cc
		14-26	Vitamin C, 150-200 mg, and orange juice
		31-55	Vitamin C, 150 mg, and orange juice
M. O.	12	4	Vitamin C, 400 mg (intravenous)
		4-7	Orange juice
		7-15	Vitamin C, 150 mg
F. W.	27	27	Orange juice, 500-1,000 cc
		28-48	Vitamin C, 200 mg (muscular), and 100 mg (intravenous)
J. Ke.	15	54	High vitamin C (muscular) and (intravenous) (chart 2)

of the plasma as well as of the urinary output (chart 2). The initial plasma level was 0.16 mg per hundred cubic centimeters. After a moderate test dose, of 275 mg, of cevitamic acid, a relatively high urinary excretion (80 mg) occurred in the subsequent twenty-four hours. After this he was given a daily oral supplement of 100 mg of cevitamic acid. Two days after the test dose the plasma level was still severely lowered (0.26 mg). In the ensuing eleven days the twenty-four hour urinary excretion of cevitamic acid ranged from 20 to 60 mg, although the plasma levels during fasting remained between 0.12 and 0.27 mg per hundred cubic centimeters. At this time, in addition to the oral supplement of 100 mg, the daily intravenous administration of vitamin C was started, as indicated in the graph. For seven days the urinary output was lower than the preceding average, and the plasma level showed no significant change. However,

there was a remarkable improvement in the clinical condition of the patient within two days after the first intravenous injection of the sodium salt of cevitic acid. The critical phase of cardiac decompensation had passed, and progressive improvement followed. This improvement was augmented later by diuresis induced with salyrgan. It is interesting that eventually a high urinary excretion occurred in spite of a persistently lowered vitamin C level of the blood. On the thirty-second day of illness a second oral test dose of 275 mg. of cevitic acid was administered. Two hours later the cevitic acid level of the plasma was 0.53 mg. per hundred cubic centimeters. The ensuing fifteen hour urinary output was high (220 mg.)

This record indicates that in certain cases of severe active rheumatic fever there may be a significant fault in the vitamin C metabolism. Although not conclusive, a record such as this suggests that the renal threshold for vitamin C may be abnormally lowered. Usually the plasma level and the urinary excretion are closely parallel,¹⁶ although this type of reaction has been observed in a few cases.

COMMENT

These data are in accord with our preliminary observation¹⁴ and with the extensive study of Abbasy, Hill and Harris¹¹ and indicate a subsaturation or suboptimal nutritional state relative to vitamin C not only in active rheumatic fever but commonly in the interval or inactive phases of the disease. The three main possibilities which suggest themselves as the basis of this are, first, a deficient intake, second, depletion by the disease itself or by preceding infection and, third, an inherent or acquired metabolic fault. It is probable that one or more of these mechanisms may operate in a given case. The work of others that has been summarized here and our own studies, we feel, strongly support the concept that vitamin C deficiency may be an integral part of the mechanism in the pathogenesis of rheumatic fever. Prolonged, well controlled and carefully judged therapeutic and prophylactic studies appear to be indicated.

Although it is known that the vitamin C level of the blood plasma in normal and most pathologic states is an index of the intake of vitamin C and gives data comparable to the data based on urinary excretion the full significance of the occasional occurrence of consistently lowered plasma levels in the face of a high intake of vitamin C is not known. No accurate data are available on the vitamin C content of connective tissue. It is possible that the latter is dependent on an adequate concentration in the blood for normal metabolism. Lowered cevitic acid levels of the blood are obviously not solely found in rheumatic fever or rheumatoid arthritis, and in individual cases they do not denote scurvy. The latter is a tissue change resulting from the operation of suboptimal

16 Greenberg, Rinehart and Phatak¹³ Rinehart, Greenberg and Christie¹⁴

or low metabolic levels over some period of time. However, the finding of practically uniformly lowered vitamin C levels in the blood in rheumatic fever, not only in the active but commonly in the quiescent phases of the disease, together with other accumulated evidence cited, strongly suggests that vitamin C deficiency exists in this disease and is of etiologic significance.

SUMMARY AND CONCLUSIONS

The cevitamic acid content of the blood plasma is practically uniformly low for patients with acute rheumatic fever if a significantly high increase in the intake of vitamin C has not been made preceding the determination. Furthermore, the majority of patients convalescent from rheumatic fever or with inactive rheumatic fever also show low blood plasma values. This study is in accord with that of Abbasy, Hill and Harris,¹¹ which was based on urinary excretion of vitamin C. Observations are cited indicating that a fundamental fault in metabolism of vitamin C exists in some cases of acute rheumatic fever. These data indicate that vitamin C deficiency commonly exists in rheumatic fever, and they add support to the concept that this deficiency may be of etiologic significance in the disease. Prolonged and carefully controlled prophylactic and therapeutic studies are indicated.

COMPLEMENT FIXATION IN AMEBIASIS

A COMPARATIVE EVALUATION IN CLINICAL PRACTICE

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AND

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The first reference to the serologic diagnosis of amebiasis was made by Izar,¹ in 1914. He experimented with complement fixation, the technic on which the Wassermann reaction for the diagnosis of syphilis is based. While sporadic studies were subsequently made, it remained for Craig² (1927) to place this test on a relatively practical basis by improving the preparation of the antigen and standardizing the technic. Later attempts to improve the Craig test resulted in minor changes by Sherwood and Heathman³ (1932), Weiss and Arnold⁴ (1934) and Tsuchiya⁵ (1934). Each of these workers or pair of workers with a different modification of the test has corroborated, in the main, Craig's contention of the specificity of complement fixation in the diagnosis of amebiasis. Details of the history and development of this procedure have been treated adequately in Craig's⁶ excellent monograph entitled "Amebiasis and Amebic Dysentery" (1934).

Read at the annual meeting of the American Society of Tropical Medicine, Baltimore, Nov. 18, 1936.

From the Gastro-Intestinal Section of the Medical Clinic of the Johns Hopkins Hospital and Medical School and the Department of Protozoology, the Johns Hopkins School of Hygiene and Public Health.

1 Izar, G. Ueber das Vorkommen spezifischer Antikörper im Serum von Amobenruhrkranken (*Entamoeba tetragena*), (supp.) Arch. f. Schiffs- u. Tropenhyg. **18** 36-39, 1914.

2 Craig, Charles F. Observations upon the Hemolytic, Cytolytic and Complement-Binding Properties of Extracts of *Endamoeba histolytica*, Am. J. Trop. Med. **7** 225-240, 1927.

3 Sherwood, N. P., and Heathman, L. Further Studies on the Antigenic Properties of Pathogenic and Free Living Amebas. Complement Fixation Tests in Amebic Dysentery, Am. J. Hyg. **16** 124-136, 1932.

4 Weiss, E., and Arnold, L. Complement Fixation Test for Amebiasis, Am. J. Digest. Dis. & Nutrition **1** 231-233, 1934, The Specificity of the Complement Fixation Test for Amebiasis, *ibid.* **1** 548-552, 1934.

5 Tsuchiya, H. Further Studies on the Cultivation of *Endamoeba histolytica* and a Complement Fixation Test for Amebiasis, J. Lab. & Clin. Med. **19** 495-504, 1934.

6 Craig, C. F. Amebiasis and Amebic Dysentery, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

Interest in amebiasis has greatly increased in recent years, especially since the epidemic in Chicago in 1933. Clinicians and workers in diagnostic laboratories have been desirous of making use of serologic methods the general principles and technic of which are familiar to them. Thus far no objective evaluation of complement fixation in amebiasis as it is employed at present in clinical practice has appeared. The present report presents and analyzes some data in this regard statistically.

PURPOSE

Hitherto practically all the work on complement fixation in amebiasis has been carried on by the originator of the improved method and by the proponents of the several modifications. It was our desire to test this procedure as a diagnostic aid in clinical practice. To this end and in order to avoid all possible bias, a cooperative investigation was undertaken by an internist, whose major interests lay in digestive diseases, a protozoologist and 3 serologists. Two of the serologists had no direct connection with the founding of the test or of its modifications. The protozoologist and the serologists were never acquainted with each other's results, and the character of each case was not divulged to them until the completion of the study. The cases investigated, with rare exceptions,⁷ called for extensive studies of the digestive tract, including special examinations of the stools. It is in this particular type of case that information derived from the complement fixation test would be most valuable to the clinician.

MATERIAL AND METHODS

Material—The clinical material on which this study is based consisted of 14 persons without symptoms and 136 hospital and private patients exhibiting some abdominal symptoms. All these persons were grouped according to the disorder presented or other criteria, as follows:

Chronic Ulcerative Colitis The patients with this disorder presented involvement of the large intestine, regional or general, including the rectum, which resulted in a sanguineous, mucosanguineous or mucopurulent exudate, with or without diarrhea, and which was due to unknown or undemonstrable factors. Those from whom *Endamoeba histolytica* was isolated but in whom specific amebicidal therapy resulted in eradication of the parasite without the obtaining of complete subjective and objective relief were regarded as having ulcerative colitis and not amebic dysentery.

Amebic Dysentery The patients with this disorder presented blood and pus in the dejecta from which *E. histolytica* was isolated and responded completely—subjectively and objectively—to specific amebicidal therapy.

Bacillary Dysentery The patients with this disorder showed the dysenteric syndrome without the presence of *E. histolytica*, and from them the Flexner bacillus was isolated.

⁷ Fourteen passers of *Endamoeba histolytica* cysts who appeared to be in good health were encountered during protozoologic surveys and were included in this study.

Indeterminate Dysentery The patients with this disorder showed the dysenteric syndrome, but the site or cause of involvement could not be demonstrated

Chronic Diarrhea The patients with this disorder had ill formed, relatively frequent bowel movements, without blood and pus

Disorders Marked by Varied Abdominal Symptoms The patients with these disorders presented long-standing, frequently indefinite and heretofore undetermined abdominal symptoms, which were sufficiently annoying or severe to cause them to seek and to permit intensive study, which were not characteristic of the aforementioned conditions and for which no causative organic disease could be found There were 4 exceptions Later, 3 of the patients were discovered to have intestinal malignant growths, and 1 typhoid The chief complaints were those of pyrosis, eructation, flatulence, distention, constipation, constipation together with a rare tendency to loose but not frequent stools, borborygmus, generalized abdominal discomfort, abdominal pain which varied as to location and severity from time to time, easy fatigability and a feeling of being "just below par" By some these complaints have been classified as indicating psychoneurosis Craig has reported similar symptoms as being due to *E histolytica*

Healthy Carriers The healthy carriers were a group of young men and women without any symptoms in whom cysts of *E histolytica* were encountered during protozoologic surveys and in whom immediately subsequent complete clinical examinations revealed no organic disease

No Diagnosis There was no opportunity given for clinical investigation in some instances, and no diagnosis was made, but cysts of *E histolytica* were encountered during a protozoologic survey

Fecal Examinations—Dejecta were submitted to the protozoologist for immediate examination, usually promptly after defecation The number of examinations recorded in table 1 indicates those made by him The protozoologic diagnoses shown are solely his own In certain instances material was taken directly from the site of involvement through the rectosigmoidoscope and was examined at once Smears stained with iron hematoxylin and cultures in the Tanabe-Chiba and Cleveland-Collier mediums were frequently prepared from this material by one of us (Dr Paulson) The iron-hematoxylin preparations and questionable cultures were observed also by the protozoologist In practically all instances more examinations of stools were made than is indicated by table 1, since frequent observations by house officers and technicians have been disregarded because it was not desired to assume responsibility for their work

Serologic Examinations—Serums were sent to one or more of three laboratories,⁸ herein designated as A, B and C Laboratory A had at different intervals the Craig, Sherwood-Heathman and Arnold antigens Laboratory B had only the Craig antigen, and laboratory C, an Arnold antigen Laboratories B and C prepared their own antigens Samples of serums were mailed to the second and third laboratories The technic employed with each antigen was that outlined by the investigator whose name is associated with the antigen These details have been adequately described in original papers and reviewed by Craig⁶

8 Laboratory A was the Albert Keidel-Joseph Earle Moore Laboratory, Baltimore For use in this laboratory Drs Sherwood and Arnold kindly submitted their own antigens, and Capt Williams sent a Craig antigen made in the Army Medical School Laboratory B was the Serologic Laboratory (in charge of Capt W C Williams) of the Army Medical School, Washington, D C Laboratory C was the Department of Pathology and Bacteriology (Prof Lloyd Arnold in charge) at the College of Medicine, University of Illinois, Chicago

TABLE 1—Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings

Case No	Diagnosis	Complement Fixation*					Stools Examined Before Therapy
		Laboratory A			Laboratory B Craig Antigen	Laboratory C Arnold Antigen	
		Arnold Antigen	Sherwood Antigen	Craig Antigen			
A At Least One Complement Fixation Test Showed a Positive reaction							
1 E Histolytica Found							
1	Amebic dysentery		4+	4+	Strongly positive		1†
2	Amebic dysentery		—	—	Weakly positive (50%)		1†
3	Amebic dysentery		—	—	50%+		2
4	Amebic dysentery 2½ mo later		—	—	—	3+	1
5	Amebic dysentery		—	—	—	4+	1
6	Amebic dysentery		—	—	—	4+	2
7	Amebic dysentery		—	—	50 60%+	3+	1
8	Amebic dysentery 2½ mo later†	4+	4+	4+	Strongly positive	4+	1
9	Amebic dysentery	4+	4+	4+	Strongly positive	4+	3
10	Amebic dysentery	—	—	—	—	4+	2
11	Amebic dysentery	—	—	—	—	4+	1§
12	Amebic dysentery	4+	4+	4+	Strongly positive	4+	1
13	Amebic dysentery	2+	2+	2+	Weakly positive	4+	3
13	Amebic dysentery	Anti comple mentary	Anti comple mentary	—	Strongly positive	—	4
14	Amebic dysentery					4+	1
15	Varied abdominal symptoms			—	Strongly positive 2+	—	1
16	Varied abdominal symptoms				Weakly positive	—	1
17	Varied abdominal symptoms			—	Weakly positive (50%)	—	1
18	Varied abdominal symptoms 5 mo later			4+	Weakly positive	—	3
18	Varied abdominal symptoms			4+	Weakly positive	—	1
19	Varied abdominal symptoms			—	Doubtful (±)	—	1
20	Varied abdominal symptoms	—	—	—	Weakly positive (50%)	—	1
21	Varied abdominal symptoms	—	—	—	Weakly positive (50%)	—	1
22	Varied abdominal symptoms			—	Weakly positive (60%)	—	1
23	Healthy carrier 3 mo later 6 mo later				Strongly positive	—	2
24	Healthy carrier				—	—	3
25	Healthy carrier				—	4+	1
26	Ulcerative colitis			2+	4+	4+	1
27	Ulcerative colitis			1+	—	—	10†
28	Chronic diarrhea			—	Doubtful +	—	2
29	Chronic diarrhea	0 1 = 3+	—	—	Anticomplementary	4+	5†
		0 05 = 2+			—	—	1§
		0 025 = 1+			—	—	—
30	Chronic diarrhea					3+	1
2 E Histolytica Not Found							
31	Chronic diarrhea		2+	1+	—	—	1†
32	Chronic diarrhea				Strongly positive	—	1
33	Chronic diarrhea			—	Doubtful (50%)	—	1
34	Chronic diarrhea			0 1 = 2+	Doubtful	—	1
				0 05 = 2+	—	—	—
				0 025 = 1+	—	—	—
35	Chronic diarrhea 2 mo later			—	Strongly positive	—	6†
	3 mo later			—	—	—	3
36	Chronic diarrhea			0 1 = anti comple mentary	Anticomplementary	—	3
				0 05 = 4+	—	—	1
37	Chronic diarrhea			—	—	4+	4†
38	Chronic diarrhea			—	Strongly positive	—	3†
39	Ulcerative colitis§	—		—	—	4+	6†
40	Ulcerative colitis			—	—	2+	1†
41	Ulcerative colitis			—	—	3+	2†
42	Ulcerative colitis 4 mo later			—	4+	—	4†
43	Ulcerative colitis			4+	4+	—	3
		0 1 = 4+	0 05 = 1+	—	—	—	1
		0 05 = 4+	0 025 = —	—	—	—	—
		0 025 = 4+	—	—	—	—	—
44	Ulcerative colitis# 16 days later	—		—	—	—	3
	18 days later	—		—	—	—	3
45	Ulcerative colitis			—	Very weakly positive	4+	3
46	Ulcerative colitis			—	Weakly positive	—	1
47	Ulcerative colitis#		4+	2+	—	2+	5†
					—	—	1†

TABLE 1—*Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings—Continued*

Complement Fixation*							
Case No	Diagnosis	Laboratory A			Laboratory B Craig Antigen	Laboratory C Arnold Antigen	Stools Examined Before Therapy
		Arnold Antigen	Sherwood Antigen	Craig Antigen			
48	Varied abdominal symptoms				Doubtful		4†
49	Varied abdominal symptoms**	—				4+	2†
50	Varied abdominal symptoms					2+	2†
51	Varied abdominal symptoms††				Weakly positive		1
52	Bacillary dysentery**			—	80-85%+		7†
53	Indeterminate type of dysentery‡				Weakly positive		7†
B Negative Reaction to Complement Fixation Test							
1 E Histolytica Found							
54	Varied abdominal symptoms	—					2
55	Varied abdominal symptoms			Anticomplementary	—		1
56	Varied abdominal symptoms				—		2
57	Varied abdominal symptoms				—		1
58	Varied abdominal symptoms				—		1
59	Varied abdominal symptoms			—	—		1
60	Varied abdominal symptoms			—	—		1
61	Varied abdominal symptoms				—	—	1†
62	Varied abdominal symptoms			—	—		1
63	Varied abdominal symptoms††	—					2
64	Varied abdominal symptoms	—			—	—	3
65	No diagnosis			—	—		3
66	No diagnosis			—	—		3
67	No diagnosis			—	—		3
68	No diagnosis			—	—		3
69	No diagnosis		—		—		3
70	Healthy carrier				—		2†
71	Healthy carrier				—		1†
72	Healthy carrier				—		1†
73	Healthy carrier				—		2†
74	Healthy carrier			—	—		1†
75	Healthy carrier	—					1
76	Amebic dysentery	—			—	—	3
77	Amebic dysentery	—					3
78	Amebic dysentery 2½ mo later‡		—	—	—		2
79	Amebic dysentery			—	—		3
80	Amebic dysentery**					—	7†§§
81	Amebic dysentery			—	—		2
82	Amebic dysentery					—	1
83	Ulcerative colitis#				—		1
84	Ulcerative colitis 6 mo later	—					1
85	Chronic diarrhea 2 mo later	—			—		3†
86	Chronic diarrhea	—		—	—		3
87	Chronic diarrhea			—	—	—	2
2 E Histolytica Not Found							
88	Chronic diarrhea			—	—		2†
89	Chronic diarrhea			—	—		3†
90	Chronic diarrhea		—	—	—		2†
91	Chronic diarrhea	—		—	—		1†
92	Chronic diarrhea				—		2†
93	Chronic diarrhea			—	—		2
94	Chronic diarrhea				—		5
95	Chronic diarrhea			—	—		1†
96	Chronic diarrhea**			—	—		2†
97	Chronic diarrhea			—	—		1†
98	Chronic diarrhea			—	—		1
99	Chronic diarrhea			Anticomplementary	—		2†
100	Chronic diarrhea			—	—		1
101	Chronic diarrhea					—	1
102	Chronic diarrhea	—					2†
103	Chronic diarrhea	—					3†

TABLE 1—Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings—Continued

Case No	Diagnosis	Complement Fixation*					Stools Examined Before Therapy
		Laboratory A			Laboratory B Craig Antigen	Laboratory C Arnold Antigen	
		Arnold Antigen	Sherwood Antigen	Craig Antigen			
104	Chronic diarrhea	—					2†
105	Chronic diarrhea	—					2
106	Chronic diarrhea	—					1†
107	Varied abdominal symptoms	—				—	1
108	Varied abdominal symptoms;‡	—			—		1
109	Varied abdominal symptoms		—	—	—		2
110	Varied abdominal symptoms			—	—		2
111	Varied abdominal symptoms			Anticomplementary	—		1
112	Varied abdominal symptoms			—	—		2†
113	Varied abdominal symptoms			—	—		2†
114	Varied abdominal symptoms		—	—	—	—	1
115	Varied abdominal symptoms		—	—	—	—	1
116	Varied abdominal symptoms		—	—	—	—	1
117	Varied abdominal symptoms				—	—	2
118	Varied abdominal symptoms				—	—	3
119	Varied abdominal symptoms	—					1
120	Varied abdominal symptoms	—					2†
121	Varied abdominal symptoms	—					2†
122	Varied abdominal symptoms	—					2†
123	Varied abdominal symptoms	—					1
124	Varied abdominal symptoms;‡			—	—		1
125	Varied abdominal symptoms					—	1
126	Ulcerative colitis					—	1
127	Ulcerative colitis				—		1†
128	Ulcerative colitis			—	—		4†
129	Ulcerative colitis			—	—		4
130	Ulcerative colitis#			—	—		3
131	Ulcerative colitis			—	—		1†
132	Ulcerative colitis			—	—		2†
133	Ulcerative colitis			—	—		4†
134	Ulcerative colitis#				—		3
135	Ulcerative colitis#					—	1†
136	Ulcerative colitis	—					3†
137	Ulcerative colitis	—					4†
138	Ulcerative colitis	—					8†
139	Ulcerative colitis	—					1†
140	Ulcerative colitis	—					4†
141	Ulcerative colitis	—					3
142	Ulcerative colitis	—					4†
143	Ulcerative colitis				—		3†
144	Ulcerative colitis		—	—	—		1†
145	Ulcerative colitis		—	—	—		1†
146	Ulcerative colitis	—					4†
147	Bacillary dysentery**			—	—		6
148	Bacillary dysentery**			—	—		2
149	Bacillary dysentery**	—					2
150	Bacillary dysentery**				—		2†

* The decimal numbers represent the fraction of a cubic centimeter of antigen employed

† Coproculture on Cleveland Collier and on Tanabe Chiba medium, smears stained with iron and hematoxylin

‡ E. histolytica was not found at this time, although the organism was present one month before

§ Coproculture on Cleveland Collier and on Tanabe Chiba medium

|| E. histolytica not found at this time

¶ With ileitis

Associated with lymphogranuloma venereum

** Eberthella paradysenteriae (Flexner) isolated from feces

†† Condition later diagnosed as typhoid

‡‡ Intestinal malignant growth

§§ Microscopic examinations were complicated by the presence of barium sulfate (Andrews, and Paulson, M. Am J M Sc 181: 102-106, 1931)

¶¶ Smears stained with iron hematoxylin

In the beginning it was planned in each case to obtain a series of multiple serologic reports based on different antigens. This design was frustrated by the shortage of antigens and serums, by the contamination and anticomplementary action of certain serums and occasionally by the nonreceipt of serologic reports.

RESULTS

General Data—The results of the clinical, serologic and parasitologic examinations in the 150 individual cases are shown in table 1 and

TABLE 2—Comparison of All Serologic and Parasitologic Findings in Various Clinical Groups

Clinical Diagnosis	Num ber of Cases	E histo- lytica Found by Micro scopic Exami nation, Percentage	Complement Fixation			Positive by Both Complement Fixation (All Positive) and Microscopic Examination, Percentage	Probability per 100 Times of Same Com bination by Chance
			Weakly Posi tive, Per centage	Strongly Posi tive, Per centage	All Posi tive, Per centage		
A Known symptoms							
Amebic dysentery	21	100 0	14 3	52 4	66 7	66 7	
Chronic diarrhea	33	18 2			33 2	9 1	33 0
E histolytica found	6		16 7	33 3	50 0		
E histolytica not found	27		11 1	18 5	29 6		
Varied abdominal symp toms	42	45 2			28 6	19 0	7 0
E histolytica found	19		31 6	10 5	42 1		
E histolytica not found	23		13 0	4 4	17 4		
Ulcerative colitis	34	11 8			32 4	5 9	42 0
E histolytica found	4		25 0	25 0	50 0		
E histolytica not found	30		10 0	20 0	30 0		
Bacillary and indetermi nate dysentery, E histo lytica not found	6	0 0	16 7	16 7	33 7		
Subtotal	136	36 8	15 4	21 3	36 8	19 9	0 1
E histolytica found	50		22 0	32 0	54 0		
E histolytica not found	86		11 6	15 1	26 7		
B No symptoms							
Healthy carriers	9	100 0	0 0	33 3	33 3		
No diagnosis*							
E histolytica found	5	100 0	0 0	0 0	0 0		
Subtotal	14	100 0	0 0	21 4	21 4		
Total	150	42 7	14 0	21 3	35 3	20 0	1 0
E histolytica found	64		17 2	29 7	46 9		
E histolytica not found	86		11 6	15 1	26 7		

* These patients were encountered during a protozoologic survey of convicts in a local penitentiary. They were not examined clinically but had not complained of ill health.

are summarized in table 2. For the 163 serums submitted for examination there were reports based on a single antigen in 70 cases, based on two antigens or from two laboratories in 62 cases, based on three antigens or from three laboratories in 19 cases and based on four antigens in 12 cases.

The average number of fecal examinations made in the cases in which positive results were obtained was 1.5 in the cases in which *E. histolytica* was not found, 2.5. As indicated in table 1, many of the examinations of fresh stools were supplemented by the inspection of smears treated with iron hematoxylin and by attempts to demonstrate the organism in either the Cleveland-Collier or the Tanabe-Chiba medium. The observations on stained smears added nothing to the results of examination of fresh material but were frequently of confirmatory interest. In 4 cases *E. histolytica* was first seen on the Tanabe-Chiba medium, in 2 of these cases there was growth on the other culture medium also. Even an approximation of efficiency in detecting *E. histolytica* in the present series can hardly be ventured. Some of the stools submitted were formed, thereby reducing the diagnostic efficiency. Others were loose, owing either to the nature of the patient's disorder or to the fact that a purge had been given in order to increase the likelihood of finding protozoa in the stools.⁹ Thus, it is to be emphasized in this as in other similar studies that while positive results of microscopic examinations for *E. histolytica* are relatively dependable, the same degree of reliability cannot be attached when organisms are not found.

Partially positive reactions, to the complement fixation test, i. e., weak, doubtful, 1+ or 2+ or a fixation of less than 75 per cent, are shown separately in tables 1 and 2, as it was subsequently found that the inclusion or exclusion of these instances in which there was a positive reaction modified the efficiency of the serologic tests in a marked though varied manner.

Comparison of Laboratory Findings in Clinical Groups—When the individual patients were combined into clinically similar groups, as, for example, those with chronic diarrhea, and when the positive diagnoses with all serologic systems were used (table 2), the groups of those in whom *E. histolytica* was found regularly showed higher ratios of positive results than did those in whom *E. histolytica* was not found. In no group or fraction of a group did it closely approach 100 per cent, and in all groups a positive reaction was reported for a number of patients in whom *E. histolytica* was not found. The differences in the ratios of the positive results for the various groups are not significant, owing primarily to the small numbers involved. For the total number of persons examined, however, the difference is significant, and when only patients with known symptoms of amebiasis are considered it is more highly significant, indicating that complement fixation is more successful in apprehending symptomatic than nonsymptomatic amebiasis.

⁹ Andrews, Justin. The Diagnosis of Intestinal Protozoa From Purged and Normally-Passed Stools, *J. Parasitol.* **20** 253-254, 1934.

An attempt to evaluate more critically the laboratory results with respect to the various clinical entities was made by applying the chi-square test to fourfold tables showing the association of cases in which *E. histolytica* was found with those cases in which complement fixation was positive. For this purpose the results obtained with all antigens in all laboratories were used, and partially positive results were considered as positive. As shown in table 3, this procedure gave more significant results when applied to the combined serologic data than when only strongly positive reactions were read as positive. The object was to determine for each clinical group the number of times in 100 that similar combinations of positive and negative results regarding the two attributes might be due to chance alone. The greater the probability of random assortment, the less likely it becomes that the indicated association of the attributes is meaningful and significant. The determination of the point at which purely accidental distribution stops and significant relationship begins is an arbitrary one. Most statisticians consider a probability of 4 or 5 times in 100 (i.e., equivalent to a chi-square of 4, or a difference of twice its own standard deviation) to be a practical limit to the significant concurrence of two attributes. Thus if they may occur together by sheer chance more frequently than 4 or 5 times in 100, there is little likelihood that they are significantly related, whereas if their association is shown to be one which might happen by chance less than 4 or 5 times in 100, the assumption of a significant relation is usually justified.

The data on amebic dysentery in this series are not susceptible to this type of statistical analysis, as there was deliberate selection in respect to the presence of *E. histolytica*. No dysentery was termed amebic unless organisms were found. One patient came to our attention early in the course of the disorder, and possibly the serologic tests (with negative results) were made before specific antibodies had had an opportunity to develop. This may have been the case in other instances.

In none of the other three clinical groups of patients tested does the association of positive serologic and parasitologic findings appear to be significant on the basis of the small numbers involved. Nevertheless, the computed probabilities of similar assortments by chance show that positive complement fixation reactions are less likely to have a fortuitous distribution with respect to the finding of *E. histolytica* in the case of "varied abdominal symptoms" than with either "chronic diarrhea" or "ulcerative colitis." Unless many amebic infections were not recognized parasitologically, this shows a strong tendency for falsely positive reactions to occur in ulcerative colitis, an observation which

has already been made by Sherwood and Heathman,³ Kiefer¹⁰ and Craig,¹¹ and suggests that the same may be true with regard to chronic diarrhea. It is in cases of these conditions that serologic information might be most helpful to the clinician. However, all persons studied being taken as one group, the association of positive attributes is significant, and, as indicated previously, when the group is restricted to patients with abdominal symptoms, it is even more highly significant.

Comparison of Various Technics of Complement Fixation—From the standpoint of general agreement of reports on the same antigen even in different hands, the results showed remarkable correspondence when it is considered that the antigens of the same type used in different laboratories may not have been of the same lot or of the same age. The Craig antigens reacting with the same serums in laboratories A and B agreed in 73.6 per cent of the 72 cases when partially positive reactions were regarded as positive and in 91.7 per cent when partially positive reactions were considered negative. Only 8 serums were tested with Arnold antigen in laboratories A and C. Five of these were reported as showing a negative reaction by both serologists, 3 were reported as showing a 4+ reaction in laboratory C and a negative reaction in laboratory A.

The results obtained with the Craig antigen compared favorably with those obtained with the Sherwood antigen in laboratory A. Of 29 serums tested with both, 96.6 per cent agreed when partially positive reactions were listed as positive and 89.7 per cent when they were called negative.

The Arnold antigen in laboratory C gave results which were least conformable with those based on the other antigens. Compared with the reactions obtained with the Craig antigen in laboratory B, only 54.2 per cent of the reactions agreed irrespective of how the partially positive reactions were classified.

In comparison of multiple examinations with similar or different antigens the following results were obtained. Two reports were available in each of 62 cases. With partially positive reactions considered as positive, 69.4 per cent of the reports agreed, with partial reactions considered as negative, 83.9 per cent agreed. In the 19 instances in which three reports for each were obtained, 68.4 per cent of the reports were in agreement when the partially positive reactions were considered positive and 84.2 per cent when they were classified as negative.

¹⁰ Kiefer, E. D. The Craig Complement-Fixation Test for Amebiasis in Chronic Ulcerative Colitis, *Am J M Sc* **183** 624-631, 1932.

¹¹ Craig, C. F. Further Observations upon the Complement Fixation Test in the Diagnosis of Amebiasis, *J Lab & Clin Med* **18** 873-881, 1933.

Reports based on four antigens were forthcoming in each of 12 cases, and 33.3 per cent agreed irrespective of the manner in which the doubtful results were listed.

From these considerations it appears that the complement fixation test in different hands and with different antigens gave moderately comparable results, with the exception of those reported with the Arnold antigen in laboratory C. As a general rule, greater correspondence of results was secured by grouping partially positive reactions with negative reactions.

TABLE 3—*Comparison of Results of Various Methods of Complement Fixation*

Antigen	Number of Cases	E histolytica Found by Microscopic Examination, Per centage	Complement Fixation					
			Strong Positive Reactions			All Positive Reactions		
			Positive Reactions, Per centage	Positive by Both Complement Fixation and Microscopic Examination, Per centage		Positive Reactions, Per centage	Positive by Both Complement Fixation and Microscopic Examination, Per centage	
				Probability per 100 Times of Same Combination by Chance			Probability per 100 Times of Same Combination by Chance	
Arnold								
Laboratory C	37	48.6	45.9	32.4	1.6	54.1	32.4	13.4
E histolytica found	18		66.7			66.7		
E histolytica not found	19		26.3			42.1		
Craig								
Laboratory B	110	47.3	10.9	6.4	42.4	28.2	17.7	4.5
E histolytica found	52		13.5			36.5		
E histolytica not found	58		8.6			21.7		
Craig								
Laboratory A	75	46.7	6.7	5.3	11.0	16.0	9.3	36.8
E histolytica found	35		11.4			20.0		
E histolytica not found	40		2.5			12.5		
Sherwood								
Laboratory A	31	51.6	16.1	9.7	Exceeds 50.0	25.8	16.1	48.4
E histolytica found	16		18.8			31.3		
E histolytica not found	15		13.3			20.0		
Arnold								
Laboratory A	33	24.2	0.0			0.0		
E histolytica found	9		0.0			0.0		
E histolytica not found	24		0.0			0.0		
All antigens in all laboratories	150	42.7	21.3	12.7	3.6	35.3	20.0	0.9
E histolytica found	64		29.7			46.9		
E histolytica not found	86		15.1			26.7		

A comparison of the results with the various technics of complement fixation is shown in table 3. As there was no extensive series of multiple serologic reports on the same material, relative evaluations of the probable efficiency of each method were determined by utilizing the statistical approach previously described.

Casual inspection of table 3 shows that the Arnold antigen (laboratory C) gave the highest incidence of positive serologic results in the

cases in which *E. histolytica* was demonstrated but that it also gave the highest incidence of positive results in the cases in which no amebas were found. When only strong reactions are regarded as positive, the Arnold antigen appears to give highly significant results, which is the more remarkable because of the relatively small number of cases involved. Of all the antigens used, the Arnold antigen, according to the record of positive reactions, seems to be furthest removed from chance association with *E. histolytica*. When the weakly positive reactions are included as positive, its accuracy in this series becomes less. Apparently this antigen is more sensitive than the others, showing more true positive reactions but also more false positive reactions, especially if partial reactions are considered significant. It should be noted that this antigen was prepared by the originator of the Arnold modification and was used according to the procedures developed by him in his own laboratory. This may have been an advantage not shared by the other laboratories. The fact that the Arnold antigen in laboratory A did not react with any of the serums supports this likelihood.

The Craig antigen seemed to be less sensitive than the Arnold antigen. It was slightly more successful in laboratory B than in laboratory A. Curiously, the inclusion of partially positive reactions with positive reactions in laboratory B increased its relative efficiency, whereas the same manipulation in laboratory A reduced the likelihood of significance. This directs attention to the fact that the same system, but not necessarily the employment of the same materials, in two laboratories may give diverse results, owing perhaps to the use of biologic materials of different strength or age, to apparently unimportant differences in technic or possibly to variations in interpretation, especially of borderline reactions.

The Sherwood antigen, while apparently as sensitive or more so than the Craig antigen, failed to compare favorably from the standpoint of confirming the parasitologic diagnoses.

Summarizing these findings in relation to the chi-square calculations, it is possible to list in order of decreasing significance the results of the serologic reports: (1) the Arnold antigen in laboratory C, partially positive reactions being excluded, (2) the Craig antigen in laboratory B, partially positive reactions being included, (3) the Craig antigen in laboratory A, partially positive reactions being excluded, and (4) the Sherwood antigen in laboratory A, partially positive reactions being included. It is possible, as has already been shown (table 2), that a positive reaction was associated with known amebiasis more frequently in cases of "amebic dysentery" and "varied abdominal symptoms" than in the cases of other dysenteries and diarrheas and that some of the apparent differences in the accuracy of the various sero-

logic systems may have been due to an unequal representation of the clinical types tested in each system. Nothing more than fortuitous factors influenced the distribution of the serums to the laboratories, as is indicated by the percentage of specimens examined by each laboratory from patients in whom *E. histolytica* was found (table 3) in comparison with the percentage of cases in the entire group in which *E. histolytica* was demonstrated. The specimens examined in laboratory A with the Arnold antigen constitute a minor exception, but as no positive reaction was reported, no conclusions are drawn regarding it.

COMMENT

At the outset of this study it was recognized that our experience with complement fixation in the diagnosis of amebiasis could hardly be expected to give as auspicious results as those obtained in the development and evolution of the technic. We could only hope that our experience would be fairly representative of that of the clinician who, having exhausted other facilities for the solution of differential diagnosis in some of his more perplexing cases of abdominal disorders, undertakes to obtain additional diagnostic information by sending serum to a laboratory for a report on the complement fixation with regard to amebiasis.

The disparity between the results reported and those of the original investigators was undoubtedly conditioned by a number of factors. Our clinical material was derived from hospital and private patients and in many instances was not under our complete control. While our medical colleagues were always cooperative, they were frequently satisfied with a less extensive study of stools than we desired. Some patients were available for only brief periods for a diagnostic survey. There were no opportunities for checking our results in these cases. These are difficulties inherent in clinical practice. Our serologic reports came from laboratories where the work was treated as part of the routine. It did not, therefore, in all probability, receive the special attention that it might have been accorded had it been a special research project. We have no way of estimating the original potency of the antigens used, their age or the care with which they were employed or of finding out whether special controls, such as serums known to react strongly with the antigen, were always used. However, as these laboratories make a specialty of serologic diagnosis, we can assume that their materials were used to the best advantage. The serum was in all cases obtained before therapy was instituted.

The parasitologic diagnoses were made by specialized workers in this field who had no other professional concern.

Thus our results must be interpreted as relative rather than absolute evaluations of complement fixation in amebiasis. For example, in 66·7 per cent of our cases of amebic dysentery there were positive serologic reactions, whereas Sherwood and Heathman³ reported positive complement fixation in "nearly 100 per cent," Tsuchiya⁵ in 83·3 per cent and Weiss and Arnold⁴ in 75 per cent of their respective cases. Craig¹¹ noted 3 instances of amebic dysentery in which the serologic reactions were negative. Under the circumstances it is perhaps surprising that we obtained as favorable and reasonable correlations as we did. We consider that we have subjected the technic to a most rigorous and trying test, but one which it must face if it is to be employed diagnostically in clinical practice.

To the clinician the most practical utility of the complement fixation test for amebiasis would be in assisting him to determine the etiologic factor in the dysentery-diarrihea group of diseases, especially when no other specific basis for the manifestations can be demonstrated. When all the cases studied are considered, our data reveal a statistically valid relation between the presence of complement-fixing bodies and the protozoologic evidence of amebiasis, confirming in general the specificity of the technic developed by Craig and others. However, from a practical diagnostic standpoint the test has the disadvantage of giving too many falsely positive as well as falsely negative responses, thus tending materially to vitiate its diagnostic import in an individual case. The reaction has been found to be least reliable in the clinical groups in which it might be most useful. Thus, when Kiefer¹⁰ submitted 16 serums to Craig for complement fixation for amebiasis, positive reactions were reported for 12 (75 per cent), though *E. histolytica* was not found. Craig¹¹ mentioned obtaining positive reactions in 11 cases of chronic ulcerative colitis in which amebas were not found, though he expressed the opinion that inadequate studies of the stools were made in these cases. Tsuchiya⁵ reported that in 4 (44·4 per cent) of 9 cases of nonamebic ulcerative colitis a positive reaction was obtained. Our own data (table 2) indicate that in about 30 per cent of the cases of ulcerative colitis and in a similar proportion of the cases of chronic diarrhea in which *E. histolytica* was not demonstrated a positive reaction was obtained. Thus in a considerable number of cases of acute and subacute inflammatory processes of the large bowel in which *E. histolytica* was not demonstrated there was a positive reaction with amebic antigen. The explanation previously given for this discrepancy was that the stools of these patients were not studied over a sufficiently long period to disclose the parasite or that a secondary infection was superimposed on an original amebic lesion. Both Kiefer and Craig have supported this opinion by citing instances of apparent specific responses to amebicidal therapy in cases in which complement

fixation tests showed a positive reaction. Information concerning these responses is vague and inconclusive, but it is evident that the responses are not uniform and that in many instances they are incomplete. They are hardly comparable to the dramatic abrupt recoveries usually manifested when specific antiamebic drugs are administered in cases of amebic colitis. It is questionable whether the observed rate of recovery exceeded that in cases of ulcerative colitis in which amebicidal treatment is not given but in which rest and special dietary and adjunctive symptomatic measures are employed. Chronic ulcerative colitis is a disease characterized by spontaneous intermissions or remissions and recurrences. After amebicidal therapy, which included the use of emetine hydrochloride, arsenicals and oxyquinoline derivatives, we have observed both amelioration and unimprovement in cases of ulcerative colitis in which positive and negative reactions to complement fixation tests were obtained.

Despite these observations, complement fixation in the diagnosis of amebiasis holds much promise, as evidenced by the observed concurrence of demonstrated amebiasis and positive fixation. However, improvements in antigen and in technic—both of which are likely to come—are essential before satisfactory use of the test can be made clinically. At present, for accurate diagnosis the clinician must still rely on multiple examinations of dejecta by competent observers. Indeed, Craig has stated that when adequate examinations of stools are made the test is unnecessary. The report of positive complement fixation can only direct the attention of the physician to the probability of amebiasis.

SUMMARY AND CONCLUSIONS

Serums from 150 persons studied clinically and parasitologically were submitted for complement fixation tests to one or more of three different laboratories in which one or more of three different types of specific antigens were employed.

When the patients were assembled into roughly homogeneous clinical groups, the incidence of positive results of complement fixation was regularly higher for those in whom *E. histolytica* was found microscopically than for those in whom the organism was not found. For the 150 patients considered as a whole the difference was statistically significant. For the 136 patients with symptoms it was even more highly significant, but in none of the clinical subdivisions was it statistically valid. Thus, our results confirm in general the specificity of the technic developed by Craig and others. However, from a practical diagnostic standpoint the too numerous falsely positive as well as falsely negative responses obtained under the conditions of our observation show that the test is unreliable in the individual case.

This reaction is not helpful in the cases in which it might be most useful to the clinician, in that the least significant coincidences occur in the cases of so-called indeterminate diarrhea and dysentery. In cases of chronic ulcerative colitis and chronic or intermittent diarrhea many positive reactions are obtained that are unassociated with demonstrable amebiasis.

While the general mass of serologic reports from different laboratories and with different antigens showed a fair degree of agreement, conspicuous disagreement occurred in some instances.

Of the various antigens and serologic systems employed, the most successful results, based on parasitologic diagnoses, were obtained with the Arnold antigen in Arnold's laboratory.

Statistical analysis of the partially positive reactions indicated the desirability of including them as positive reactions when obtained with relatively weak antigens and of excluding them from consideration when obtained with very sensitive antigens.

We are of the opinion that complement fixation is at present a diagnostic aid of adjunctive rather than of primary value. Its more successful application in clinical practice awaits further refinement. It should not be relied on as a diagnostic criterion unsupported by parasitologic evidence of infection. Notwithstanding the many defects of microscopic fecal diagnosis of amebiasis, this method is today more dependable than complement fixation.

NOTE—Since this paper was accepted for publication, two reports have appeared to which reference must be made for completeness. Meleney and Frye¹² have pointed out that the test is still in its developmental stage, that many infections with *E. histolytica* were associated with positive complement fixation reactions, that a significant number of patients harboring "*E. histolytica* in the intestine gave negative complement fixation reactions." They concluded that a "positive complement fixation reaction in man is presumptive evidence of the presence of ameba in the tissues and that most infected persons giving a negative reaction (except those in the early stage of the infection) harbor the parasite only in the lumen of the intestine without tissue invasion." They dismiss their positive complement fixation reactions in ulcerative colitis when *E. histolytica* was not found as probably amebic in origin because of marked clinical improvement on administration of carbarsone. This phase of the question has already been discussed elsewhere in this paper.

12 Meleney, Henry E., and Frye, William W. Practical Value and Significance of the Complement Fixation Reaction in Amebiasis, *Am J Pub Health* 27: 505-510, 1937.

Weiss and Arnold¹³ have reported important changes in their modification of the complement fixation test for amebiasis resulting in a high correlation of positive reactions with the finding of *E. histolytica* and in negligibly few false positive responses in controls. Unfortunately, there are no specific data as to the reactions of serums from those with nonamebic intestinal involvement to this altered procedure. Its use after the manner of the several procedures employed in this study seems essential before the latest Weiss-Arnold modification can be adequately evaluated in clinical practice.

13 Weiss, Emil, and Arnold, Lloyd. A Complement Fixation Test for Amebiasis with an Increased Antibody Content, *Am J Digest Dis & Nutrition* 4: 282-287, 1937.

HYPERINSULINISM AND CEREBRAL CHANGES

REPORT OF A CASE DUE TO AN ISLET CELL ADENOMA OF THE PANCREAS

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In insulin hypoglycemia, or hyperinsulinism, whether spontaneous or induced, the manner in which the nervous system is affected is of primary interest. This has been investigated (1) in "insulin shock" of patients suffering from diabetes, (2) in spontaneous hypoglycemia due to neoplasm or to hypertrophy or functional oversecretion of the islands of Langerhans and (3) under experimental conditions. We wish to report a case of spontaneous hypoglycemia due to an adenoma of the islands of Langerhans. On the basis of our study of this case and a survey of the literature, an attempt will be made to correlate the clinical, laboratory and anatomic data on this disorder from the pathogenic standpoint.

REPORT OF CASE

History—A P, a married woman aged 30, was admitted to the Ypsilanti State Hospital on March 16, 1936. The family history and the patient's past history were essentially unimportant. She had been in good health until 1930, when she began to have "fainting spells." These frequently occurred in the morning, were usually followed by a "craving for sweets" and were relieved by food. There was a gradual change to convulsive attacks, which were initiated by excessive perspiration and flushed facies. She consumed large amounts of sweets and gained rapidly in weight. In the intervals between attacks she was normal until November 1934, when the convulsions became more frequent and a definite mental change occurred. She became irritable, resistive and impulsive. This was followed by gradual emotional and mental decline. In July 1935 and again in February 1936 the patient was admitted to a private hospital in a semicomatose state. She was out of touch with her surroundings and restless, had convulsions and was incontinent. On her second admission to the hospital the fasting level for blood sugar was found to be 60 mg per hundred cubic centimeters, with 37.5 mg of sugar per hundred cubic centimeters of spinal fluid. No definite diagnosis was made, and the patient was transferred to the Ypsilanti State Hospital.

From the Laboratory of the Neuropsychiatric Institute, University of Michigan, Dr. Raymond W. Waggoner, director, and the Ypsilanti State Hospital, Dr. George F. Inch, superintendent.

Status on Admission to the Hospital—The patient was confused, restless and negativistic. She uttered peculiar cries but remained otherwise mute. There were marked generalized rigidity, drooling, excessive perspiration and incontinence of urine and feces. Otherwise the neurologic and general physical examinations revealed no abnormality.

Laboratory Data—The urine contained 1+ albumin and many white blood cells but no sugar. Examination of the blood disclosed 5,200,000 red cells and 13,150 white cells per cubic millimeter, with 81 per cent neutrophils, 12 per cent lymphocytes and 7 per cent monocytes, the hemoglobin value was 90 per cent (Sahli). The Kahn tests of the blood and spinal fluid gave negative results. Simultaneous tests of the blood and spinal fluid during fasting revealed 35 mg of sugar per hundred cubic centimeters of blood and 17.5 mg of sugar per hundred cubic centimeters of spinal fluid. Chemical examination of the blood showed cholesterol, 174.4 mg, calcium, 10.6 mg, and phosphorus, 5 mg, per hundred cubic centimeters.

In table 1 (condensed from table 2) are shown the results of sixteen determinations of the initial fasting level of the blood sugar made on different days. The high incidence of marked hypoglycemic levels (ten of sixteen readings) is obvious.

TABLE 1—*Fasting Levels of Blood Sugar*

Sugar, Mg per 100 Cc	Number of Determinations	Range of Oral Temperature, Degrees F
30-40	6	97.8-98.8
40-50	4	98.0-99.0
50-60	3	98.6-99.0
60-70	1	98.6
94	1	99.4
130	1	100.0

The normal and high readings were associated with fever. The blood sugar level after a twenty-four hour fast was not lower than that after the usual fasting period. It was noted also that active resistiveness during venipuncture tended to raise the fasting level.

The results of the various dextrose tolerance tests are given in table 2. With a normal diet, other conditions (dextrose dosage, temperature and nonadministration of sedatives) being constant, the type of curve obtained was consistently characterized by a rise in the blood sugar level, which was maintained through the two hour period, and by a delay in fall to hypoglycemic levels (the "plateau type" of curve). In the accompanying chart (fig 1), two such curves (*a* and *b*) are illustrated and represent the variations which occur in typical curves even under standard conditions. Also included in this chart is a typically "diabetic curve" (*c*) which was associated with a change in the factor of temperature (100 F), even though the other conditions remained the same. With the high carbohydrate diet, the maximum rise was not quite so pronounced, but the subsequent fall was not lower than that shown with the previous normal diet. Nevertheless, it was noted that the convulsions had their onset during the period of high intake of carbohydrate. The low carbohydrate diet could not be carried out for a sufficiently prolonged period for adequate study.

Two types of hepatic function tests were made. 1. In order to test the adequacy of the glycogen stores, the patient was given on three occasions injec-

TABLE 2—Fasting Level of Blood Sugars and Dextrose Tolerance Tests

Date	Fasting Level	Hours						Temperature (Oral) Range, Degrees F.	Diet
		1/2	1	1 1/2	2	2 1/2	3		
3/24	35.0							98	Normal
3/26	31.0	190.0	250.0	215		190	170.0	98.6-98.8	Normal
3/27	37.9							98	Normal
3/28	57.0							99	Normal
3/29	46.37							98.98-1	Normal
4/1	68.3	181.6	181.6					98.6-99	Normal
4/9	58.6-42							98.6-98.8	Normal
4/11	39.2							98.2-99	Normal
4/17	91.0							99.1-101	Normal
4/22	11.0							98.6-98.8	High carbohydrate
4/25	11.0							98.97-8	High carbohydrate
5/28	31.0							97.8-98.2	Normal
5/29	51.0							98.98-8	Normal
6/16	36.3							100	Low carbohydrate
7/3	130.0							99.99-6	
7/6	48.0								

* The dose of dextrose given was 1 Gm per kilogram of calculated average body weight, the customary 175 Gm per kilogram given at first (on March 26) produced vomiting. All the determinations of the blood sugar were carried out on venous blood after the method of Folin and Wu, and the results are given in milligrams per hundred cubic centimeters.

tions of epinephrine hydrochloride, the results are recorded in table 3. These demonstrate that there was apparently an adequate amount of glycogen present for mobilization. It was most strikingly shown during the test made on April 9. On this date, although an attempt was made to deplete the glycogen store of the liver by twenty-four hours of starvation, the response was in every way comparable to the responses to the other tests. 2. The bromsulphalein test showed a retention of less than 15 per cent on two occasions. The bilirubin content of the blood was 0.2 mg per hundred cubic centimeters. The icterus index was 9.

Comment—An islet cell neoplasm of the pancreas was suspected because of the high ("plateau") type of sugar tolerance curve obtained, the consistently severe hypoglycemia and the absence of adrenal, thyroid or pituitary dysfunction. However, disease of the liver could not definitely be ruled out, in spite of the negative

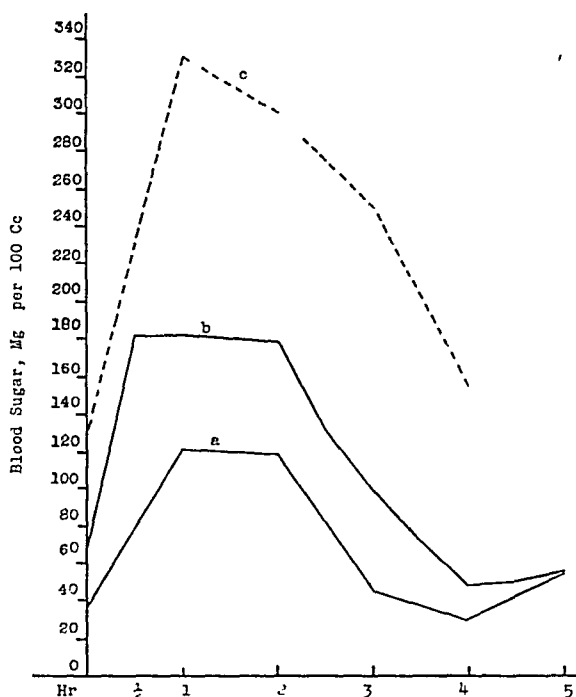


Fig 1—Dextrose tolerance curves

results of the hepatic function tests. An exploratory operation on the pancreas did not appear justified, since there was no change in the clinical picture when the blood sugar was maintained at an approximately normal level for long periods by dietary measures. Moreover, the patient was obviously a poor "operative risk."

Clinical Course—Throughout her stay in the hospital the patient remained semistuporous, mute, negativistic, restless and incontinent of urine and feces. It was noted that at times she blinked her eyes or closed one eye when attempting to look at any one, suggesting the presence of diplopia. Arthritis deformans, with contractures of the fingers, gradually developed. On June 12 the patient suddenly became pale, drowsy and restless, her eyes closed and her lips drooped. This seizure lasted for twenty minutes. Two days later she had an attack lasting for three minutes, which began with a peculiar cry and was followed by spasmodic jerking of the trunk and arms, frothing at the mouth, a staring expression, dilatation of

the pupils, perspiration and stertorous breathing. On June 18 there was another attack, with cyanosis, drooling, tonic and clonic spasms of the whole body followed by a staring expression, loud snoring and continuous swallowing movements. A similar attack occurred the following day. The next seizure occurred on July 2, but the convulsions changed from a generalized to a jacksonian type. This was characterized by spasmodic twitchings, which spread along the right upper extremity and occasionally involved the right side of the face and right lower extremity, the eyes deviating variously to the right and to the left. This type of seizure persisted without interruption until two weeks before death. At the same time cystitis developed and the temperature rose to 102 F per rectum, remaining elevated until death occurred. On July 31 the convulsions suddenly ceased, and the patient gradually sank into a deep coma. On August 13 the temperature rose to 106.5 F, and signs of bronchopneumonia developed. Blood sugar determinations were in the neighborhood of 200 mg per hundred cubic centimeters just before the patient expired.

Necropsy—Ten minutes after death, hepatic tissue was removed and macerated in 20 per cent solution of potassium hydroxide for a determination of the glycogen content. The average reading obtained was 0.5 per cent hepatic glycogen.

TABLE 3—*Response During Fasting of Blood Sugar Content to Epinephrine* *

Date	Blood Sugar, Mg per 100 Cc			Oral Temperature, Degrees F
	Initial Value	½ Hour After Injection of Epinephrine	1 Hour After Injection of Epinephrine	
3/28/36	57	115.3	181.0	99
3/29/36	46.37	111.0	169.9	98.98.4
4/ 9/36	58.6.42	92.0	170.0	98.6.98.8

* Injections of 1 cc of 1:1,000 solution of epinephrine hydrochloride were given during fasting.

determined as dextrose-reducing substance.¹ Within two and one-half hours the complete necropsy was performed. The body appeared well developed and fairly well nourished. There were contractures of both hands. The pancreas was of normal size and had an essentially normal external appearance. However, section revealed a solitary yellowish spherical encapsulated tumor, measuring 1.1 by 0.9 by 1 cm, and embedded within the head of the pancreas near its junction with the body. The liver had a fatty, nutmeg appearance. A tumor the size of a small walnut was seen in the thyroid gland, multiple small cysts surrounded the left ovary. There were, in addition, bronchitis, bronchopneumonia and generalized passive congestion.

The microscopic examination of the tumor in the pancreas revealed an encapsulated adenoma consisting of tissue closely resembling normal structure of the islands of Langerhans (fig 2A). The epithelial tissue was arranged either in long convoluted cell cords or in the form of tubules about capillaries (fig 2B). The cells were cuboid or cylindric, with large vesicular darkly staining nuclei. The epithelial cells were in intimate contact with the capillaries, and there was no membrana propria. A delicate connective tissue stroma traversed the tumor, and a well defined fibrous capsule surrounded it. Otherwise, the pancreas disclosed a moderate increase in the number of islands of Langerhans which were, how-

1 This test was performed by Dr J. W. Conn, of the Department of Internal Medicine, the University of Michigan.

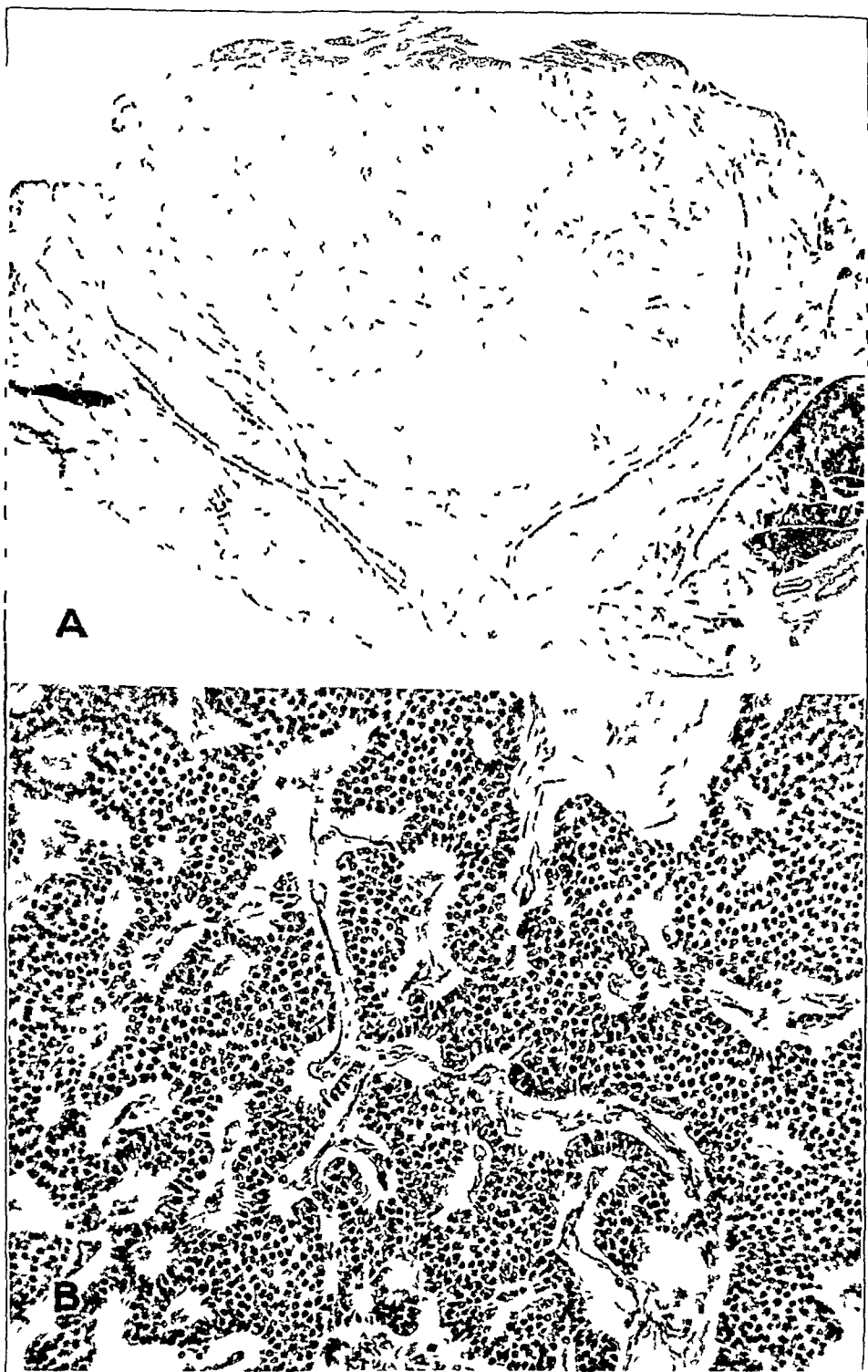


Fig 2—*A*, encapsulated islet cell adenoma, with moderate hyperplasia of the islands of Langerhans in the surrounding pancreas. Hematoxylin and eosin stain photomicrograph, Zeiss planar, 50 mm. *B*, higher magnification of *A*, showing the architecture of the tumor. The tissue is composed of a syncytium of cords and tubules of epithelial cells arranged about capillaries. Hematoxylin and eosin stain photomicrograph. Zeiss objective 16 mm, projection ocular, no 2.

ever, not hypertrophied, the acinous tissue, the blood vessels and the connective tissue stroma were normal. In the liver there were scattered focal accumulations of lipoids in the form of fatty infiltration and degeneration. The latter occurred chiefly in congested and atrophic lobules about the central veins, there was no increase in the amount of connective tissue. There was lipoidosis of the cortex of the adrenal glands.² The tumor in the thyroid gland was histologically a colloid cystic adenoma. In the hypophysis there was diffuse eosinophilic hyperplasia, and a small basophilic adenoma was seen in the anterior lobe. There were, in addition, chronic catarrhal endocervicitis, old hyaline corpora fibrosa in the ovaries, purulent bronchitis and early bronchopneumonia, moderate brown atrophy of the myocardium, early phlegmon of the breast and passive congestion of the spleen, liver, kidneys, lungs and gastro-intestinal tract.

The brain weighed 1,125 Gm. The leptomeninges were thin and moderately congested, the basal vessels were delicate. The convolutions were well developed. In coronal sections the cortex was for the most part well demarcated from the white matter and moderately hyperemic, but in the left hemisphere there were scattered areas in which the gray matter was narrow and appeared spongy. The ventricles were of normal width, and the ependyma was smooth. The basal ganglions, brain stem, cerebellum and cervical portion of the spinal cord were grossly normal. The pineal gland was cystic.

In the pia-arachnoid there was slight fibroblastic thickening. The meningeal vessels were moderately distended and congested but otherwise normal.

In the cerebral cortex of both hemispheres there was distinct universal parenchymatous degeneration, more pronounced in the left hemisphere and varying in intensity in different regions. The most striking feature of the degenerative process was its laminar character, which was noted throughout the gray matter. Layers 3 and 5 were most commonly and severely involved. In some areas the degeneration extended also into layers 2 and 6, whereas the fourth layer was usually well preserved. In the first layer there was considerable gliosis. On the whole, the laminar degeneration could be subdivided according to the degree and sequence of involvement into the following types: (1) paling (*Eibleichung*) of laminae 3 and 5, with neither appreciable loss of nerve cells nor glial reaction (fig 3A), (2) moderate degeneration of laminae 3 and 5, with loss of neurons and beginning glial reaction, chiefly microglial, (3) severe degeneration of laminae 3 and 5, accompanied with pronounced gliosis and varying involvement of laminae 2 and 6 (fig 3B), and (4) severe destruction of all layers except the fourth, associated with cortical atrophy and status spongiosus.

Examination of the left hemisphere revealed that the cortex of the frontal lobe was moderately involved (type 1), severe laminar degeneration being restricted to the gyrus cinguli. Starting with the precentral region and extending posteriorly throughout the entire hemisphere, the degeneration was severe (types 3 and 4) in both the isocortex and the allocortex. In the latter the nucleus amygdalae and the uncus were completely degenerated. In the cornu ammonis the involvement was selective, the fascia dentata being well preserved, but the end-plate and the resistant part were completely degenerated (fig 4). Sommer's sector was relatively well preserved, but there was increasing severity of the degeneration in the subiculum and presubiculum, which merged with that of the temporal lobe. In the right hemisphere in contrast to the picture on the left side, there was uniformly mild

² The organs of internal secretion and the reproductive organs were examined by Prof. Carl V. Weller, of the Department of Pathology, the University of Michigan.

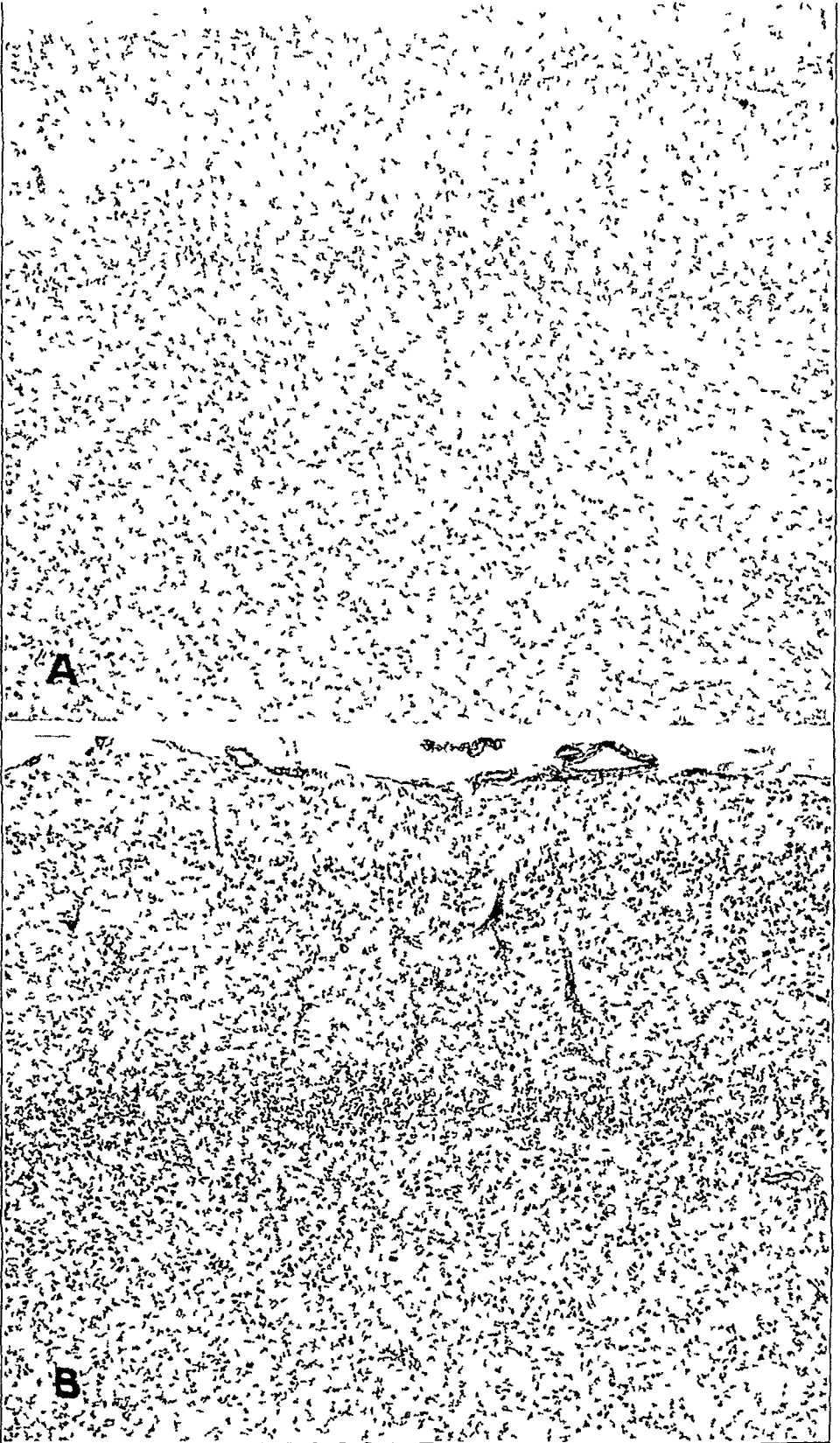


Fig 3—*A*, cortex of the right parietal region, showing laminar paling (*Erbleichung*) of the parenchyma in layers 3 and 5. Nissl stain, photomicrograph, Zeiss planar, 20 mm. *B*, cortex of the left parietal region, showing laminar degeneration and gliosis involving layers 3 and 5 and encroaching on layers 2 and 6. Nissl stain, photomicrograph, Zeiss planar, 20 mm.

involvement of type 1 in the entire gray matter, with the exception of the gyrus cinguli, where the degeneration was similar to that of the left side

The changes in the neurons were predominantly those of "Nissl's acute swelling" The cells and their dendrites were swollen, there was chromatolysis of the tigroid substance and the cytoplasm was homogeneous and pale The nuclei were swollen, but their structure remained otherwise intact The neurofibrils were disintegrated in the center but were preserved at the periphery of the cell and in the dendrites The cells contained occasional lipid droplets In severely degenerated areas the neurons were either reduced to shadows or completely destroyed "Nissl's severe change," incrustation and inflated elements were rare The axis-cylinders were reduced in number, frequently fragmented and

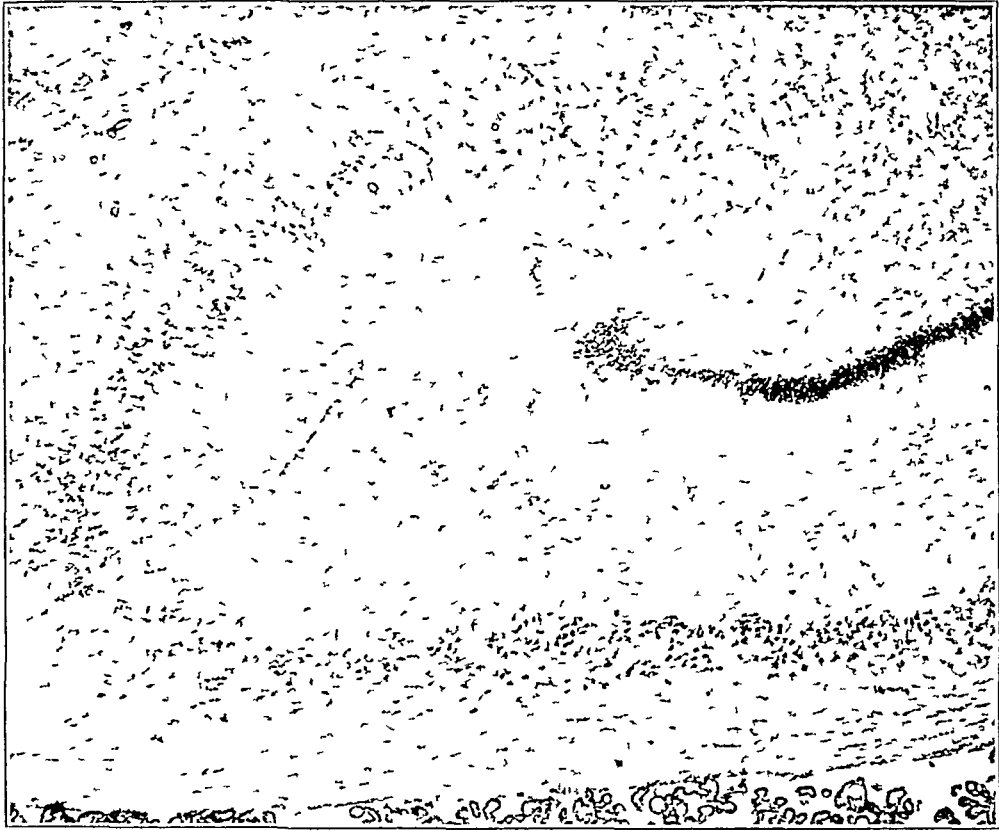


Fig 4—Cornu ammonis of the left hemisphere Note the selective involvement of the resistant part and end-plate and the preservation of Sommer's sector Nissl stain, photomicrograph, Zeiss planar, 20 mm

swollen Weigert preparations showed demyelination and reduction of the tangential and radial fibers of the cortex In less involved regions the microglia was greatly proliferated and contained considerable lipid deposits, whereas in severely degenerated areas the astrocytes predominated, forming a dense glial network There was also an increase in marginal, subependymal and perivascular gliosis There were regressive changes in the oligodendroglia, neuronophagia was common in degenerated areas The blood vessels contained a few droplets of fat in the adventitia but were otherwise essentially normal There was no iron

The white matter was essentially normal, with only slight rarefaction in the myelin sheaths and moderate increase in the number of glial fibers The choroid plexus and the ependyma were normal

Examination of the basal ganglions showed distinct changes in the caudate nucleus and putamen of each side, more pronounced on the left, disclosing diffuse degeneration of the small ganglion cells, whereas the large ganglion cells were well preserved, there was moderate proliferation of the glia. There were no significant changes in the pallidum. The thalamus was severely involved bilaterally, especially in the left pulvinar, in which the neurons were greatly reduced in number and the microglia and macroglia were proliferated.

In the corpus Luyssi, hypothalamus, brain stem, cerebellum and cervical portion of the spinal cord there was only diffuse swelling of the neurons.

REVIEW OF THE LITERATURE

A Clinical Observations—From a clinical standpoint the symptoms of hyperinsulinism are variable and have been so well outlined by a number of authors that they will be only briefly referred to here. According to Wilder,³ the symptoms may be classified into (1) disorders of the vegetative nervous system (perspiration, salivation and changes in heart rate), (2) organic neurologic symptoms (convulsions, periods of coma and focal signs) and (3) psychopathologic manifestations (psychoneuroses and psychotic states). Bowen and Beck⁴ concluded that the initial symptoms are vegetative phenomena caused by "epinephrine discharge" (Cannon) and followed by manifestations referable to the central nervous system.

B Laboratory Observations—The various laboratory data on "spontaneous" hyperinsulinism reported in the literature will be considered according to four general etiologic groups: (1) neoplasms of the islands of Langerhans, (2) hypertrophy or hyperplasia of the islands of Langerhans, (3) hyperinsulinism ameliorated by partial resection of the normal pancreas and (4) functional hyperinsulinism generally benefited by dietary therapy. For the first two groups the etiology is established, in the third it is highly suggestive but in the last group it is problematic. In accordance with this classification, table 4 (page 595) includes a grouping of the dextrose tolerance curves in ninety-nine cases reported in the literature, as well as the type of response to epinephrine when recorded.⁵

The dextrose tolerance curves reported are here arbitrarily subdivided into two distinct types: (a) the high, sometimes "plateau" or even "diabetic" type of curve, which is characterized by an initial rise,

³ Wilder, J. Zur Neurologie und Psychiatrie der hypoglykämischen Zustände, *Med Klin* **26** 616 (April 25) 1930.

⁴ Bowen, B. D., and Beck, G. Insulin Hypoglycemia, *Ann Int Med* **6** 1412 (May) 1933.

⁵ This review was restricted to articles in English. The cases of hypoglycemia reported by P. J. Cammidge (*Hypoglycemia*, *Lancet* **2** 1277 [Dec 20] 1924, *Chronic Hypoglycemia*, *Brit M J* **1** 818 [May 3] 1930) are not included, because that author said he did not regard them as due to hyperinsulinism.

usually abrupt, and is invariably maintained above the average normal fasting level for blood sugar through the two hour period before the eventual return to hypoglycemia sets in (delayed hypoglycemic response), and (b) the low, sometimes flat type of curve, which occasionally shows a definite rise within the first hour but is always well below the average normal fasting level for blood sugar by the second hour, when it is often definitely hypoglycemic (accelerated hypoglycemic response). The two unclassified tests included in table 4 are not characteristic of either *a* or *b*, in that they show a delayed rise occurring between one and one-half and two hours, which is often considered as signifying a delay in the absorption of the dextrose. Such variable factors as previous diet, temperature dosage of dextrose and medication which alter the dextrose tolerance test, are frequently not mentioned in the literature. Therefore, one must assume in such a classification that the patient with hyperinsulinism had at least an adequate amount of carbohydrate in his diet, that he did not have fever or did not need sedative medication and that a standardized dose of dextrose was given for the test. The various results of the dextrose tolerance test will be discussed further presently.

In general, the reported average fasting level for blood sugar is low particularly for the groups of patients with neoplasm and hypertrophy of the islet cells, but occasionally it is relatively normal.

The response to epinephrine is considered to be adequate when within an hour after the injection there is a rise of the blood sugar level from hypoglycemic to normal or higher levels, usually with the relief of symptoms. Occasionally, in the absence of determinations of the blood sugar level, the response is thought adequate if the symptoms are quickly and adequately relieved.

Other hepatic function tests in these cases, such as the injection of bromsulphalein or phenoltetrachlorophthalein, the van den Bergh reaction and the determination of the bilirubin content of the blood gave normal results when reported⁶ except in two cases (Rynea^{6a} and Judd,

6 (a) Wilder, R. M., Allen, F. N., Power, M. H., and Robertson, H. E. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, *I. A. M. A.* **89** 348 (July 30) 1927. (b) Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. L. Dysinsulinism. Convulsions and Coma Due to Islet-Cell Tumor of the Pancreas with Operation and Cure, *ibid.* **93** 674 (Aug. 31) 1929. (c) Carr, A. D., Parker, R., Grove, E., Fisher, H. O., and Larrimore, I. W. Hyperinsulinism from Beta Cell Adenoma of the Pancreas, Operation and Cure *ibid.* **96** 1363 (April 25) 1931. (d) Womack, N. A., Gnagi, W. B., and Graham, E. A. Adenoma of the Islands of Langerhans with Hypoglycemia. Successful Operative Removal, *ibid.* **97** 831 (Sept. 19) 1931. (e) Bast, T. H., Schmidt, E. R., and Severinghaus, E. L. Pancreatic Tumor with Hypoglycemia Status Epilepticus, *Acta chir. Scandinav.* **71** 82, 1932. (f) Derick, C. L.,

Faust and Dixon⁶¹) in which hepatitis was present at biopsy. Adequate amounts of glycogen in the liver were reported by Wilder and his associates,^{6a} McClenahan and Norris,⁷ and Cragg, Power and Lindem⁶¹ Terbruggen⁸ and Rienhoff and Lewis,^{6k} on the other hand, observed no glycogen in the liver on histologic examination

Newton, F C , Schutz, R Z , Bowie, M H , and Pokorny, N A Spontaneous Hyperinsulinism, *New England J Med* **208** 293 (Feb 9) 1933 (g) Graham, E A , and Womack, N A The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and to Other Conditions, *Surg , Gynec & Obst* **56** 728 (April) 1933 (h) Wolf, A , Hare, C C , and Riggs, H W Neurological Manifestations in Two Patients with Spontaneous Hypoglycemia with Necropsy Report of Case of Pancreatic Island Adenoma, *Bull Neurol Inst New York* **3** 232 (June) 1933 (i) Ziskind, E Hyperinsulinism Report of Case of Spontaneous Hypoglycemia with Studies in Dextrose Tolerance, *Arch Int Med* **52** 76 (July) 1933 , personal communication to the authors (j) Ross, L I , and Tomasch, J M Hyperinsulinemia, Secondary to an Adenoma of the Pancreas Report of a Case with Operative Cure, *Arch Surg* **28** 223 (Feb) 1934 (k) Rienhoff, W F , Jr , and Lewis, Dean Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1889 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans, and a Case of Pancreato-Lithiasis, *Bull Johns Hopkins Hosp* **54** 386 (June) 1934 (l) Judd, E S , Faust, L S , and Dixon, R K Carcinoma of the Islands of Langerhans with Metastasis to the Liver Producing Hyperinsulinism, *West J Surg* **42** 555 (Oct) 1934 (m) Whipple, A O , and Frantz, V K Adenoma of Islet-Cells with Hyperinsulinism, *Ann Surg* **101** 1299 (June) 1935 (n) Feiner, L , Soltz, S E , and Haun, P The Syndrome of Adenoma of the Pancreas, *Bull Neurol Inst New York* **4** 310 (Oct) 1935 (o) Liu, S H , Loucks, H H , Chou, S K , and Chen, K C Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, *J Clin Investigation* **15** 249 (May) 1936 (p) Kepler, E J , and Walters, W Chronic Hypoglycemia Caused by Hyperinsulinism Cure Effected by Removal of Adenoma of Pancreas, *Proc Staff Meet, Mayo Clin* **11** 454 (July 15) 1936 (q) Ryneerson, E H Adenoma of the Islands of Langerhans Two Cases, *ibid* **11** 451 (July 15) 1936 (r) Long, C F , Sheplin, L , and Fishbach, D B Spontaneous Hyperinsulinism Due to Pancreatic Adenoma in a Patient with Carcinoma of the Sigmoid A Catastrophic Conjunction, *Am J Digest Dis & Nutrition* **3** 488 (Sept) 1936 (s) Aitken, L F Diagnosis and Treatment of Hyperinsulinism, *M Clin North America* **20** 393 (Sept) 1936 (t) McCaughan, J M , and Broun, G O The Value of Partial Pancreatectomy in Convulsive States Associated with Hypoglycemia, *Ann Surg* **105** 354 (March) 1937 (u) Lukens, F W , and Ravdin, I S Adenoma of the Islet Cells of the Pancreas with Operation and Recovery, *Am J M Sc* **194** 92 (July) 1937 (v) Cragg, R W , Power, M H , and Lindem, M C Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, *Arch Int Med* **60** 88 (July) 1937

7 McClenahan, W U , and Norris, D W Adenoma of the Islands of Langerhans with Associated Hypoglycemia, *Am J M Sc* **177** 93 (Jan) 1929

8 Terbruggen, A Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome, *Beitr z path Anat u z allg Path* **88** 37 (Nov 19) 1931

C Pathologic Observations—In cases of spontaneous hypoglycemia due to neoplasm or to hyperplasia or hypertrophy of the islands of Langerhans little pathologic change was observed in other organs of the body. In most instances the liver was essentially normal. Changes in the central nervous system have been reported in only a few cases of proved islet cell neoplasm. These consisted of cerebral edema and congestion (Thalheimer and Murphy,⁹), perivascular round cell infiltration in the meninges and brain (McClenahan and Norris⁷), atrophy of the cortex and fatty degeneration of the ganglion cells (Terbruggen⁸), moderate diffuse loss of ganglion cells from the cortex (Wolf and his associates^{6h}) and scattered hemorrhages (Baker and Lufkin¹⁰).

For several patients who died in "insulin shock," cerebral changes have been reported. Macroscopically, Wohlwill¹¹ described a dry flaccid brain, other authors (Bowen and Beck,⁴ Bodechtel¹² and de Morsier and Mozer¹³) noted cerebral edema. The histologic changes varied from moderate to severe diffuse degeneration of the ganglion cells in the cortex and basal ganglia. Bodechtel¹² emphasized the focal occurrence of the changes and the prevalence of Spielmeyer's "homogeneous cell disease" in his case. Others (Wohlwill¹¹ and Terplan¹⁴) described "Nissl's severe change" in the neurons and swelling phenomena of the glia and axis-cylinders.

Experimentally, a number of investigators were able to produce definite pathologico-anatomic changes by induced hyperinsulinism. Schereschewsky and his co-workers¹⁵ noted necrosis in the adrenal glands, lipoidosis of the liver and kidneys, generalized edema, congestion and hemorrhages, and degeneration of the neurons in the sympathetic and central nervous systems. The authors placed particular emphasis on the changes in the sympathetic system. According to Stief

9 Thalheimer, W., and Murphy, F. D. Carcinoma of Islands of Pancreas Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **91** 89 (July 14) 1928.

10 Baker, A. B., and Lufkin, N. H. Cerebral Lesions in Hypoglycemia, *Arch. Path.* **23** 190 (Feb.) 1937.

11 Wohlwill, F. Ueber Hirnbefunde bei Insulin-Ueberdosierung, *Klin. Wchnschr.* **7** 344 (Feb. 19) 1928.

12 Bodechtel, G. Der hypoglykamische Schock und seine Wirkung auf das Zentralnervensystem zugleich ein Beitrag zu seiner Pathogenese, *Deutsches Arch. f. klin. Med.* **175** 188, 1933.

13 de Morsier, G., and Mozer, J. J. Lésions cérébrales mortelles par hypoglycémie au cours d'un traitement insulinique chez un morphinomane, *Ann. de med.* **39** 474 (May) 1936.

14 Terplan, K. Changes in the Brain in a Case of Fatal Insulin Shock, *Arch. Path.* **14** 131 (July) 1932.

15 Schereschewsky, N. A., Mogilnitzky, B. N., and Gorjaewa, A. W. Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, *Endokrinologie* **5** 204, 1929.

and Tokay,¹⁶ both diffuse and focal types of parenchymatous degeneration can be produced in the cortex and basal ganglions, the severity and the acuteness of the changes being directly proportional to the dosage of insulin and the duration of its administration. Similar pathologic observations were reported by Grayzel,¹⁷ who said he believed that the severity of the changes depended on the frequency and intensity of the convulsions.

D Pathogenesis—Regarding the mechanism of injury to the central nervous system, opinions differ as to whether the hypoglycemia, the insulin per se or other disturbances of metabolism are the responsible factors. On the basis of experimental data, two theories have been postulated (1) anoxemia and (2) disturbed water balance.

1 *Theory of Anoxemia* Olmsted and Logan,¹⁸ in an early report, observed that the arterial blood in insulin hypoglycemia was venous in character, and they compared the effects of hyperinsulinism to those of asphyxia. They assumed that "anoxemia of the brain through a depressant effect of the hypoglycemia" was responsible for the convulsions. Dameshek, Myerson and Stephenson¹⁹ arrived at similar conclusions after obtaining by the "internal jugular method" during a severe insulin reaction a marked diminution in the normal arterio-venous difference in the content of oxygen, signifying a reduction in the uptake of oxygen by the brain. However, in a later study, Olmsted and Taylor²⁰ found that after the administration of insulin there is only a slight fall in the oxygen saturation of the arterial blood preceding the convulsion. They concluded that the convulsions cannot be attributed to the "mild anoxemia" but that both phenomena are directly caused by the insulin.

2 *Theory of Disturbed Water Balance* Drabkin and Ravdin²¹ reported that in previously dehydrated animals, insulin in doses suffi-

16 Stief, A., and Tokay, L. Beitrage zur Histopathologie der experimentellen Insulinvergiftung, *Ztschr f d ges Neurol u Psychiat* **139** 434, 1932. Weitere experimentelle Untersuchungen uber die cerebrale Wirkung des Insulins *ibid* **153** 561, 1935.

17 Grayzel, D. M. Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, *Arch Int Med* **54** 694 (Oct.) 1934.

18 Olmsted, J. M. D., and Logan, H. D. Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, *Am J Physiol* **66** 437 (Oct.) 1923.

19 Dameshek, W., Myerson, A., and Stephenson, C. Insulin Hypoglycemia, *Arch Neurol & Psychiat* **33** 1 (Jan.) 1935.

20 Olmsted, J. M. D., and Taylor, A. C. Effect of Insulin on the Blood. Changes in Oxygen Saturation, Percentage Hemoglobin and Oxygen Capacity, *Am J Physiol* **69** 142 (June) 1924.

21 Drabkin, D. L., and Ravdin, I. S. The Mechanism of Convulsions in Insulin Hypoglycemia, *Am J Physiol* **118** 174 (Jan.) 1937.

cient to cause hypoglycemia failed to produce convulsions or to influence the pressure of the cerebrospinal fluid. On the contrary, in previously hydrated animals a rise in the pressure of the cerebrospinal fluid and in the incidence of convulsions regularly occurred. The authors concluded that insulin convulsions occur only when the sequence of hypoglycemia, anhydremia and a rise in the pressure of the cerebrospinal fluid takes place and said they considered the anhydremia as the most important factor in the mechanism of the convulsions.

Comment. These theories have been applied to explain the anatomic changes in the nervous system. Thus, Bowen and Beck¹ interpreted their findings of cerebral edema as an effect of anhydremia in the sense accepted by Diabkin.²¹ Other authors have attributed the changes to the hypoglycemia either directly through diminished nutrition (Terbruggen,⁸ and Wolf, Hare and Riggs^{6b}) and the anoxemia effect on the brain tissue or indirectly by causing vasospasm in the sense accepted by Spielmeyer (Bodechtel,¹² Stief and Tokay,¹¹ Grayzel¹⁷ and de Moissier and Mozei¹³). Thus, Bodechtel¹² compared the histologic picture with changes produced by ligating the carotid arteries and with other "circulatory disturbances." He attributed the focal lesions, the type of neuronal alteration ("homogeneous cell disease") and the occasional capillary hemorrhages to spasm or stasis of the blood vessels. According to Stief and Tokay,¹⁶ pathologic changes in the brain can be produced experimentally only by subcutaneous and cisternal but not by intracerebral injections of insulin. This the authors said they regarded as proof for the vascular action of the hypoglycemia, as opposed to a direct irritant effect of the insulin. Schereschewsky and his associates¹⁵ suggested that the mechanism is partly vasomotor through changes in the sympathetic system and partly a direct toxic action of insulin on the central nervous system. Wohlwill¹¹ attributed the cerebral changes to alkalosis.

GENERAL COMMENT

Our case represents a typical example of hyperinsulinism due to islet cell adenoma. The clinical course of convulsive attacks, focal neurologic signs and atypical psychotic manifestations demonstrates the variability in the symptomatology in such cases. Certain clinical features that have not been sufficiently emphasized in the literature are significant. It has been generally regarded that the episodic course of the symptoms is characteristic of the disorder. In our case, however, this initial phase was gradually replaced by permanent organic dementia. Again, the relief of symptoms with the elevation of the blood sugar to normal or higher levels, so characteristic of this condition, was not found in our case. It seems reasonable to believe that in the initial phases of the disease the pathologic effects are of a reversible order and can be relieved by dietary or surgical therapy. With the progress of the dis-

order, however, permanent impairment of cerebral functioning that is no longer amenable to therapy may take place. This is corroborated in our case by the pathologico-anatomic changes.

The extremely variable results of the reported laboratory tests,²² as reviewed, make their interpretation difficult. In attempting to explain the paradoxical dextrose tolerance curves, Weil^{22j} stated the opinion that the curve varies with the type of lesion in the pancreas. Thus, he concluded that the high, almost diabetic curve is characteristic of carcinoma of the islet cells, that the moderately high and prolonged curve is suggestive of adenoma and that the low, flat curve is typical of "functional" hyperinsulinism when there are no demonstrable structural changes. Feiner and his associates^{6a} said they regarded the plateau type of curve as characteristic of islet cell adenoma. However, further analysis reveals that such a relation is not consistent. Table 4 shows that

22 (a) Harris, S. Hyperinsulinism and Dysinsulinism, *J A M A* **83** 729 (Sept 26) 1924, Hyperinsulinism and Dysinsulinism (Insulogenic Hypoglycemia) with Chronological Review of Cases Reported in the United States and Canada, *Endocrinology* **16** 29 (Jan-Feb) 1932, Hyperinsulinism, a Definite Disease Entity. Etiology, Pathology, Symptoms, Diagnosis, Prognosis, and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyperinsulinism), *J A M A* **101** 1958 (Dec 16) 1933, Epilepsy and Narcolepsy Associated with Hyperinsulinism, *ibid* **100** 321 (Feb 4) 1933, Clinical Types of Hyperinsulinism. Case Reports, *Am J Digest Dis & Nutrition* **1** 562 (Oct) 1934. (b) Nielsen, J M, and Eggleston, E L. Functional Dysinsulinism with Epileptiform Seizures, Treatment, *J A M A* **94** 860 (March 22) 1930. (c) Winans, H M. Chronic Hypoglycemia, *South M J* **23** 402 (May) 1930. (d) Waters, W C, Jr. Spontaneous Hypoglycemia. The Role of Diet in Etiology and Treatment, *ibid* **24** 249 (March) 1931. (e) Marsh, H E. Hyperinsulinism, with Report of a Case, *Wisconsin M J* **30** 340 (May) 1931. (f) Gammon, G D, and Tenerv, W C. Hypoglycemia. Clinical Syndrome, Etiology and Treatment. Report of a Case Due to Hyperinsulinism, *Arch Int Med* **47** 829 (June) 1931. (g) Moore, H, O'Farrell, W R, Malley, L K, and Moriarity, M A. Acute Spontaneous Hypoglycemia, *Brit M J* **2** 837 (Nov 7) 1931. (h) Shepardson, H C. Glycopenia. The Efficacy of High Fat Diets in the Treatment of Chronic Hypoglycemia, *Endocrinology* **16** 182 (March-April) 1932. (i) McGovern, B E. Epileptoid Attacks and Hyperinsulinism. Report of a Case, *ibid* **16** 293 (May-June) 1932. (j) Weil, C K. Functional Hyperinsulinism. Epileptiform Convulsions, Accompanying Spontaneous Hypoglycemia, *Internat Clin* **4** 33 (Dec) 1932. (k) Sippe, C, and Bostock, J. Hypoglycemia. A Survey and an Account of Twenty-Five Cases, *M J Australia* **1** 207 (Feb 18) 1933. (l) Graham and Womack^{6g}. (m) Tedstrom, M K. Hypoglycemia and Hyperinsulinism, *Ann Int Med* **7** 1013 (Feb) 1934. (n) Clark, B B, and Greene, J A. Effect of Low Carbohydrate Diet on the Glucose Tolerance in Spontaneous Hypoglycemia, *Proc Soc Exper Biol & Med* **32** 1459 (June) 1935. (o) Powell, E. The Story Behind Two Blood Sugar Curves (Hypoglycemia as a Cause of Mental Symptoms), *Tri-State M J* **8** 1612 (March) 1936. (p) McCullagh, E P. Treatment of Chronic Hypoglycemia, *M Clin North America* **19** 2005 (May) 1936. (q) MacBryde, C M. Borderline Endocrine Disturbances, *ibid* **20** 337 (Sept) 1936.

there were five instances of the low type of curve in cases of proved islet cell neoplasm, two instances of the high type of curve in cases in which a normal pancreas was seen at operation and six instances of the high curve in cases of functional hyperinsulinism

We believe that the type of dextrose tolerance curve furnishes an index of the degree of the severity of the disorder, regardless of the

TABLE 4—*Summary of Data on Dextrose Tolerance Curves Reported in Literature*

Etiologic Factor	Dextrose Tolerance Curves, Number of Cases			Epinephrine Response, Number of Cases	
	High	Low	Unclassified	Adequate	Inadequate
1 Neoplasms of islet cells *	21	5	1	12	3
2 Hypertrophy or hyperplasia of islet cells †		3	1		
3 Resection of normal pancreas ‡	2	7		3	
4 Functional hyperinsulinism §	6	53		7	1

* Footnote 6

† Simon, H E Surgery in the Treatment of Hyperinsulinism, South Surgeon 3: 211 (Sept) 1934 McCaughan and Broun^{6†}

‡ Finney, J M T, and Finney, J M T, Jr Resection of the Pancreas, Tr Am S A 46: 268, 1923, Ann Surg 88: 584 (Sept) 1923 Harris, S Epilepsy and Narcolepsy Associated with Hyperinsulinism, J A M A 100: 321 (Feb 4) 1933 The Diagnosis of Surgical Hyperinsulinism, South Surgeon 3: 199 (Sept) 1934, Clinical Types of Hyperinsulinism Case Reports, Am J Digest Dis & Nutrition 1: 562 (Oct) 1934 Holman, E, and Rallsback, O O Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia, Surg, Gynec & Obst 56: 591 (March) 1933 Graham, E A, and Hartmann, A F Subtotal Resection of the Pancreas for Hypoglycemia ibid 59: 474 (Sept) 1934 McCaughan and Broun^{6†} Womack, N A, and Cole, W H The Thyroid Gland in Hypoglycemia, Ann Surg 105: 370 (March) 1937

§ Footnote 22

TABLE 5—*Relation of Dextrose Tolerance Curve to Severity of Disorder*

Etiologic Factor	Symptoms	Number of Cases	Dextrose Tolerance Curve		
			High	Low	Unclassified
Neoplasm	Severe	23	21	1	1
	Mild	4		4	
Hypertrophy and hyperplasia	Mild	4		3	1
Resection of normal pancreas	Severe	2	2		
	Mild	7		7	
Functional hyperinsulinism	Severe	7	6	1	
	Mild	52		52	
Total	Severe	32	29	2	1
	Mild	67		66	1

type of lesion in the pancreas In table 5 an attempt has been made to illustrate such a relation Here the same dextrose tolerance tests recorded in table 4 are tabulated in relation to the type of symptom found in each instance, the symptoms being arbitrarily classified as severe or mild The severe type of disorder is characterized by frequently recurring convulsions, prolonged periods of coma and other severe neuropsychiatric symptoms or requires dextrose therapy approximately every two hours to prevent attacks In such cases the dextrose tolerance curve is predominantly of the high type In the milder form

the symptoms consist of fleeting periods of unconsciousness or abnormal behavior. The relief obtained from dextrose is of longer duration. Convulsions are not prominent, but occasionally hypoglycemia may precipitate a latent convulsive disorder. In these cases in which the symptoms are mild the dextrose tolerance curve is consistently of the low or flat type.

The factors underlying these curves are complex and still obscure. It is known that the high type of dextrose tolerance curve is also characteristic of hypoglycemia resulting from hepatic disease or from experimental extirpation of the liver. Further, it is obtained also with starvation or with a diet low in carbohydrate, when it is attributed more clearly to a depletion of the hepatic glycogen. These facts suggest that the high and diabetic types of dextrose tolerance curves in cases of severe hyperinsulinism point to a complicating hepatic factor which would at least partially explain the otherwise unexpected high curve. This is to be understood in the sense of physiologic disturbance rather than as actual structural change in the liver. The latter is usually lacking, as in our case. Hepatic function tests and the response to epinephrine in hyperinsulinism vary considerably and frequently fail to indicate involvement of the liver or the adequacy of glycogen storage. In our case for example, in which the response to epinephrine was adequate and hepatic function tests gave normal results, the glycogen content was markedly diminished, even though this may have been partly caused by the terminal increased metabolism associated with the fever before death. An evaluation of these findings is as yet impossible, in view of the paucity of reports of hepatic glycogen determinations in the literature. In the few reports available, the glycogen content was said to be either adequate or greatly diminished. The question still remains whether in severe hyperinsulinism the liver is depleted of glycogen or whether the glycogen is so firmly fixed in the liver by the excess insulin that a normal response to ingestion of dextrose is not obtained. On the other hand, in cases of milder hyperinsulinism, in which the curve is low or flat, one can picture an insulin-liver mechanism which is overworking in much the same manner as it does in response to the stimulus of increased intake of carbohydrate (Sweeney²³ and Himsworth²⁴). The flat type of curve is also obtained at times in cases of hypo-adrenalism, hypothyroidism and hypopituitarism in which there is a normal insulin-secreting mechanism but a diminished concentration of insulin antagonists. One can consider that in these cases there is mild relative hyperinsulinism associated with the fundamental disease.

23 Sweeney, J. S. Dietary Factors That Influence the Dextrose Tolerance Test. A Preliminary Study, *Arch Int Med* **40** 818 (Dec.) 1927.

24 Himsworth, H. P. Dietetic Factor Determining Glucose Tolerance and Sensitivity to Insulin of Healthy Men, *Clin Sc* **2** 67 (Sept.) 1935.

Thus, it is suggested that the response to ingestion of dextrose in the cases of mild involvement is that of a well coordinated overactive mechanism, while in the severe forms, in which there is a high type of curve, the insulin-liver mechanism is functioning incoordinately. Our case, in which there were a consistently high type of dextrose tolerance curve and marked depletion of the hepatic glycogen, serves to illustrate the latter and is clearly correlated with the severe clinical and pathologico-anatomic conditions.

The anatomic basis for the clinical manifestations in our case is evident in the advanced destruction of the cortex, thalamus and striatum. The greater involvement of the left cerebral hemisphere apparently accounts for the contralateral jacksonian attacks. This is a unique example of severe pathologic effects on the brain in a case of hyperinsulinism. The outstanding feature of the anatomic changes is their purely parenchymatous degenerative character. All the characteristics of a primary toxic degenerative process are obvious from the direct and diffuse effect on the parenchyma, beginning with "acute swelling" of the neurons and paling of the tissue and progressing to ultimate degeneration, to which the glia reacts secondarily. The condition is analogous to primary degenerative diseases of the central nervous system and to encephalopathies due to exogenous toxins (for instance, morphine or nitrous oxide). It suggests a direct toxic effect of some substance elaborated in hyperinsulinism. One may speculate here about the possibility that the excess insulin in the blood may act as such a toxic substance.

In view of the complexity of insulin metabolism, such an assumption is supported mainly by indirect evidence. For, as previously mentioned, the phenomena of hypoglycemia, anoxemia, anhydremia, alkalosis and other metabolic disturbances accompanying hyperinsulinism have been held responsible for the cerebral changes. It remains to be seen whether any of these are the essential factors in this disorder and are capable of producing such pathologic effects on the brain.

The primary role attributed to the hypoglycemia has been questioned in view of the lack of parallelism between the level of the blood sugar and the clinical manifestations. It is also known that drugs which have no appreciable effect on the blood sugar level can be used therapeutically as antidotes in insulin shock (Popper and Jahoda²⁵). The cerebral changes which have been attributed to the hypoglycemia, on the assumption of either its vasospasmodic action or its anoxic effect, cannot be confirmed here. While both diffuse and focal changes have been observed in animal experimentation and in cases of fatal

²⁵ Popper, L., and Jahoda, S. Coffeinwirkung bei hypoglykämischen Zuständen. *Klin Wchnschr* 9 1585 (Aug 23) 1930.

insulin shock, undue emphasis has been placed on the focal changes and the entire condition attributed to vascular spasm, in the sense accepted by Spielmeyer. It seems to us that these changes are merely local accentuations of the diffuse process. In our case the characteristics of such vasomotor disturbances as discontinuous focal areas of necrosis and ischemic changes in the nerve cells are entirely lacking. In the cornu ammonis the resistant part is degenerated, not Sommer's sector, as would be expected in vascular conditions. Moreover, the widespread laminar distribution of the degeneration cannot be attributed to vascular factors (Braunmuhl²⁶). Also, changes in the electrocardiogram, pulse rate and blood pressure in this disorder are said to confirm a vascular etiology. However, it is still disputed whether these cardiovascular effects are produced by the hypoglycemia or by insulin toxicity (Hadorn²⁷).

For similar morphologic reasons, comparisons with cerebral anoxemia are untenable. As outlined by Gildea and Cobb,²⁸ the pathologic picture of acute cerebral anoxemia following ligation of the carotid arteries consists predominantly of necrobiotic foci and characteristic changes in the ganglion cells (shrunken cells, cells with spikelike processes). In chronic anoxemia the white matter because of its lower consumption of oxygen, is more involved than the gray matter (Putnam²⁹), whereas in this disorder the white substance is spared. Undoubtedly, impaired oxidation of the brain accompanies the hypoglycemia, but this does not explain the clinical manifestations (Olmsted and Taylor²⁰) nor the histopathologic changes.

It seems unlikely that hydration of the central nervous system (in the sense of Diabkin) can produce such a clinicopathologic picture. For, although the experiments of Diabkin and Ravdin²¹ demonstrate a relation between convulsions and anhydremia induced by insulin, other clinical manifestations remain unexplained. Pathologico-anatomically, one would expect that cerebral edema would be more frequent in hyperinsulinism than is actually the case. Moreover it is doubtful whether edema can produce such degeneration of nerve tissue.

26 Braunmuhl, A. V. Picksche Krankheit, in Bumke, O. Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

27 Hadorn, W. Das Herz in Insulinschock, Schweiz. med. Wchnschr. **39** 936 (Sept.) 1936.

28 Gildea, E. F., and Cobb, S. The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23** 876 (May) 1930.

29 Putnam, T. J. The Cerebral Circulation. Some New Points in Its Anatomy, Physiology and Pathology, J. Neurol. & Psychopath. **17** 193 (Jan) 1937.

SUMMARY

A case of chronic hypoglycemia due to an islet cell adenoma of the pancreas is reported with clinical laboratory and pathologico-anatomic data

The clinical course of convulsions, psychotic manifestations and organic dementia is correlated with the advancing destruction of the cerebral cortex and basal ganglions

The diffuse degeneration of the brain is interpreted as a direct toxic effect of insulin on the parenchyma

It is suggested that the dextrose tolerance test in cases of hyperinsulinism is an index of the severity of the pathologico-physiologic process This is to be understood as a change in the insulin-liver mechanism regulating dextrose metabolism

CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

IV OBLITERATING PULMONARY ARTERITIS WITH SECONDARY PUL- MONARY CHANGES AND RIGHT VENTRICULAR HYPERTROPHY, REPORT OF A CASE WITH AUTOPSY

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AND

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NEW YORK

Thrombo-angitis obliterans, or Buerger's disease, is a well recognized clinical entity. In the majority of cases the condition is localized in one group of arteries,¹ but in some cases it may even invade neighboring veins, in the form of phlebitis migrans. Obliterating arteritis on the other hand, is confined to the smallest arterioles, without involvement of the venous system. Hence, these two conditions must be considered apart pathologically and clinically.

Despite the fact that obliterating arteritis is a rare disease, the recent clinical significance attributed to it warrants reporting a case in which we have had the opportunity of following the disease from onset to termination.

REPORT OF CASE

D P, a man aged 33, experienced sudden pain in the chest, with dyspnea, six months before admission to the hospital. He consulted his family physician, but the only objective findings were tachypnea and tachycardia. He continued to work, with periodic confinement to bed, until he had lost 20 pounds (9 Kg) and had become so weak that he was no longer able to continue in his occupation.

On Jan 8, 1934, he was seen by his family physician in consultation with Dr I W Held, and he said that although he experienced pain in the chest on exertion, this was not as troublesome as the shortness of breath. The chief findings were tachypnea, tachycardia, moderate cyanosis of the lips and fingers

† Dr Rothschild died on Feb 16, 1936

Aided through the Henry Dazian Fund

From the Department of Medicine and the Department of Pathology, the Beth Israel Hospital

1 (a) Birnbaum, Walter, Prinzmetal, Myron, and Connor: Charles L. Generalized Thrombo-Angitis Obliterans. Report of a Case with Involvement of the Retinal Vessels and Suprarenal Infarction, *Arch Int Med* **53** 410 (March) 1934. (b) Horton, Bayard T, Magath, Thomas B, and Brown, George E. Arteritis of the Temporal Vessels, *ibid* **53** 400 (March) 1934.

without clubbing and a rapid pulse. The eyes were staring, but the blood pressure was not increased. There was no orthopnea. Examination of the chest revealed a few sibilant rales at the bases of the lungs, with diminished breathing over the base of the left lung. On auscultation a split first sound and an accentuation of the pulmonic second sound were noted. Fluoroscopic examination showed the apex of the heart in the midclavicular line. The pulmonary artery was not dilated. Over the base of the left lung there was a dense area suggestive of pneumonitis, and the left interlobar pleura was thickened, with restriction of diaphragmatic movement on the left. In the second oblique position there was density in the midportion of the retrosternal space suggestive of thickening of the mediastinal pleura.

The diagnosis seemed to lie between coronary thrombosis (*sine dolore*), with an infarct in the left ventricle, and a mediastinal mass (Hodgkin's disease) pressing on the vagus nerve. Of the two conditions, it seemed more likely that the former was the cause of the patient's symptoms, particularly in view of the thickened pleura and the strong suggestion of a secondary pulmonary infarct. The absence of glandular enlargement did not favor a diagnosis of Hodgkin's disease of the thorax.

On January 11 the patient entered the hospital on the service of one of us (Dr. Rothschild). The symptoms and physical findings were unchanged except that the heart sounds gave an impression of a gallop rhythm. However, a phonocardiogram showed only a split first sound and no true gallop rhythm.

Laboratory Data—The blood count showed 16,900 leukocytes, with 81 per cent segmented cells. The red blood cell count and the hemoglobin values were normal. The sedimentation rate was 27 and 45 per cent, respectively, on two occasions. Chemical analysis of the blood showed 35 mg of lactic acid per hundred cubic centimeters (increased). The calcium and phosphorus values were normal.

The basal metabolic rate was 37 and 27 per cent, respectively, on two occasions.

A cardiodynamic study revealed the following: venous pressure, 4 cc, circulatory time (saccharine method), thirteen seconds, plasma volume, 2,813 cc, total blood volume, 5,228 cc, oxygen consumption, 300 cc, arteriovenous oxygen difference (calculated from the dissociation curves of the blood), 50 cc, cardiac output, 6 liters (calculated value, 4.82 liters),² and vital capacity, 2,300 cc.

The oxygen dissociation curve was normal, with marked diminution of the saturation of blood starting at about 8 volumes per cent and dropping to 3 volumes per cent (fig. 1). The arterial oxygen saturation was 50 per cent of normal (figs. 2 and 3).

The electrocardiographic study showed a regular rhythm of 100 beats per minute, a normal P-R interval, a diphasic T₁ wave, a diphasic T₂ wave and an abnormal lead IV, in that there was an upright T₄ wave (anteroposterior method). These findings suggested myocardial damage (fig. 4).

Roentgenographic study of the chest by Dr. I. Seth Hirsch revealed diffuse interstitial changes involving both lungs and not associated with the marked congestion. The pleura of the middle and lower lobes of the right lung was

² The increased cardiac output (6 liters) is of no significance because of the marked tachypnea and the difficulty with which the alveolar samples were collected. The true value of the cardiac output calculated from the blood volume showed no increase (Goldbloom, A. Allen, and Roht, Paul K. Cardiac Output Values from Calculated Blood Volume unpublished data).

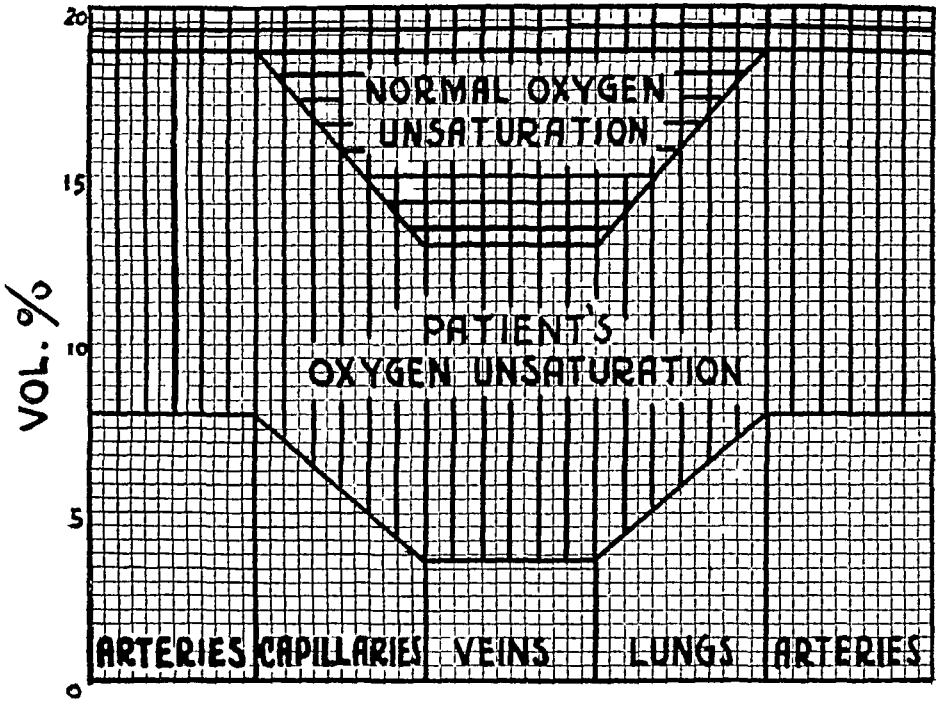


Fig 1—Oxygen unsaturation of the blood

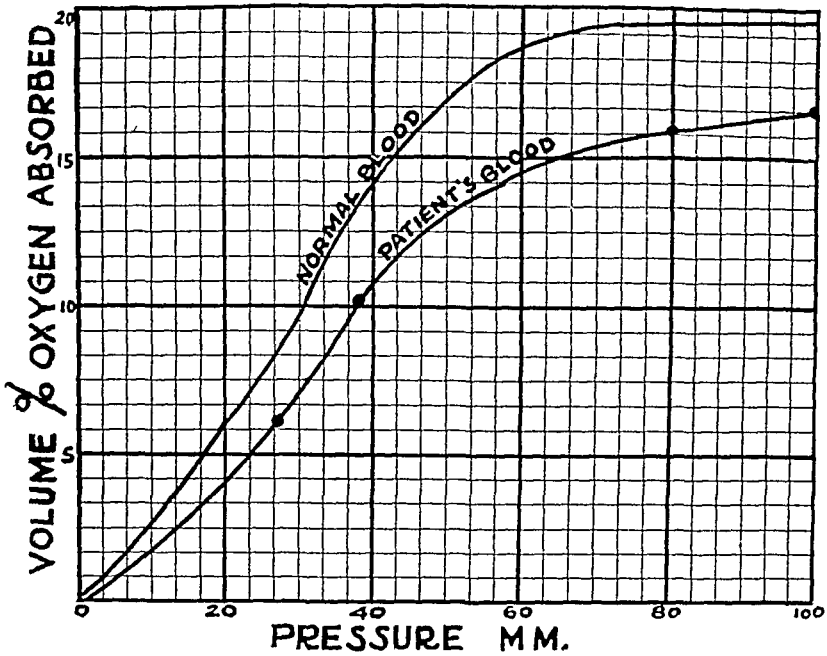


Fig 2—Oxygen dissociation curve The carbon dioxide pressure was 40 mm

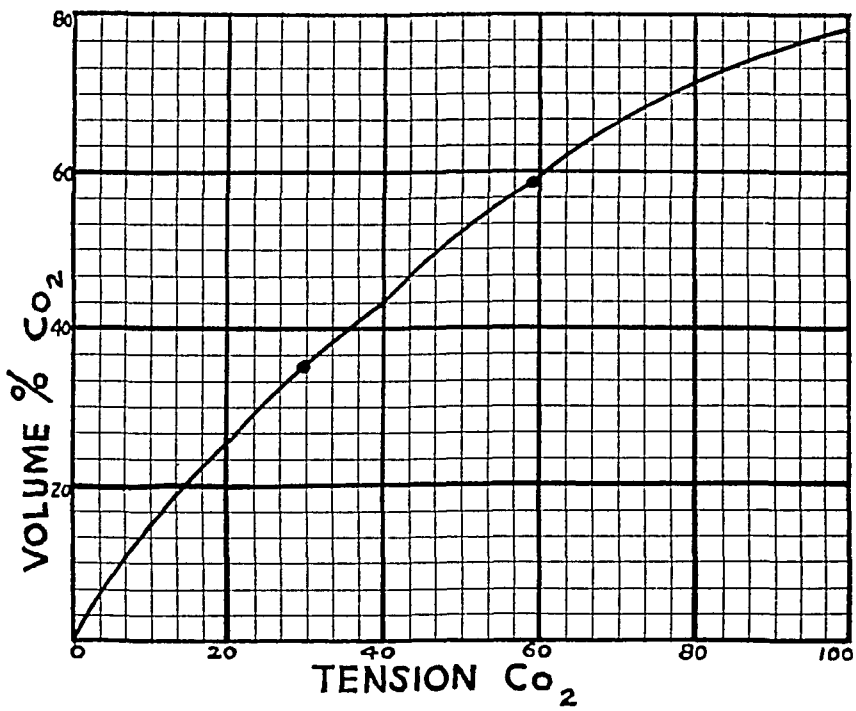


Fig 3—The carbon dioxide absorption curve for oxygenated whole blood

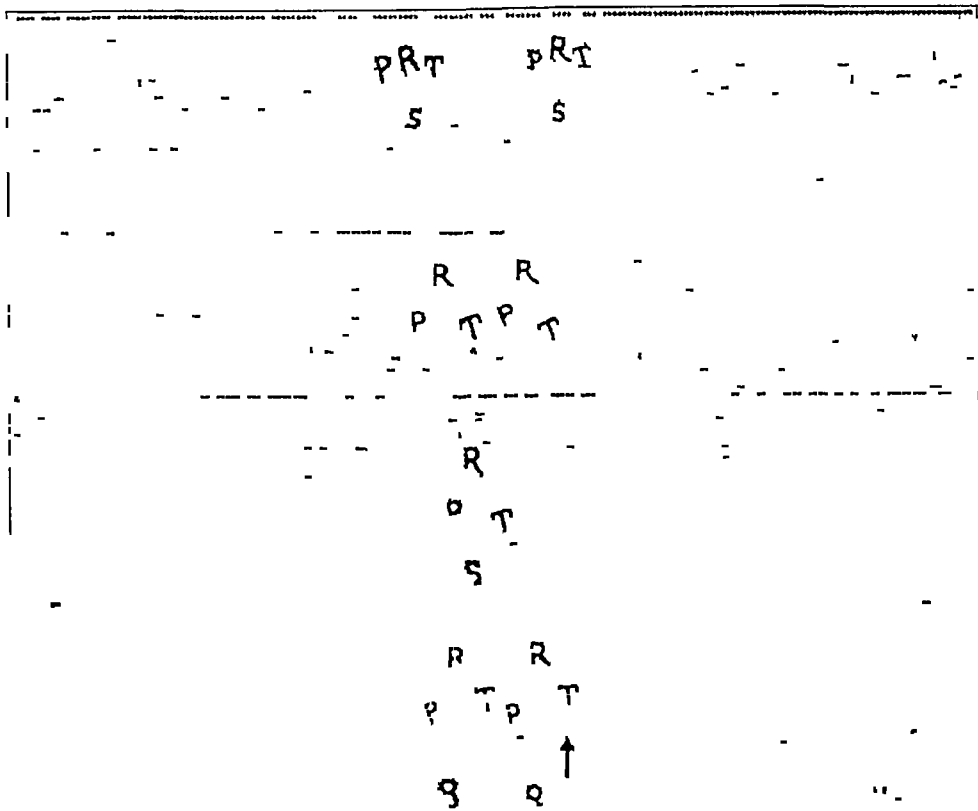


Fig 4—Electrocardiographic tracings

markedly thickened, and there was a small amount of effusion in the pleural cavity. The left ventricle was enlarged. The mediastinum was normal. The most striking features were the diffuse congestion and the interstitial changes in the lower lobe of the right lung.

Roentgenograms of the phalanges showed no periostitis or thickening of the soft tissues.

Bronchoscopic examination by Dr J. Miller revealed no abnormality.

Diagnosis—Although there was electrocardiographic evidence of myocardial damage (fig 4), the cardiodynamic studies (normal blood volume and circulatory time) tended to rule out a coronary condition as the direct cause of the myocardial damage. Hodgkin's disease was finally ruled out by the normal roentgenographic and bronchoscopic findings. Thyrotoxicosis, likewise, was eliminated as a possibility by the fact that the blood volume, circulatory time and cardiac output were not increased, as they usually are in this condition.³

On the basis of the clinical picture, namely, cyanosis, tachycardia, tachypnea and no orthopnea (closely resembling the symptoms in the case reported by Frothingham⁴) and also because of the diminished oxygen saturation, indicating some obstruction in the arterial system, the condition was diagnosed (by Dr Rothschild) as due to an infection, with primary involvement of the pulmonary arterioles.

Progress—The tachypnea and cyanosis continued. The temperature rose to 101 F, the pulse rate was 120 and the respiratory rate was 44. Evidence of failure of the right side of the heart increased. Oxygen and digitalis treatment were of no avail. Two days before death occurred pulmonary edema developed with acute failure of the left ventricle. The patient died on February 4, three weeks after admission to the hospital.

*Gross Postmortem Examination*⁵—The postmortem diagnosis was obliterating arteritis of the small pulmonary arteries, partly thrombo-arteritis, dense pleural adhesions, and hypertrophy of the right ventricle.

The pericardium was normal. The pulmonary arteries were free. The right side of the heart was distinctly hypertrophied. The coronary arteries were normal.

In the middle of the upper lobe of the left lung there was a firm, round, irregularly outlined mass directly beneath the pleura. The latter was thickened and hyperemic. The interlobar space was obliterated. Another firm indefinitely circumscribed area was situated near the lower edge. No distinct circumscribed lesions were seen in the pulmonary artery. Incision of the lungs revealed a number of

3 Goldbloom, A. Allen. Diagnostic Importance of Blood Volume and Cardiac Output Studies in a Borderline Case of Thyrotoxicosis, *M. Clin. North America* **17** 279, 1933. Goldbloom, A. Allen, Libin, I., and Roht, Paul K. Clinical Studies in Circulatory Adjustments. I. Clinical Evaluation of Studies of Circulating Blood Volume, *Arch. Int. Med.* **55** 484 (March) 1935. Goldbloom, A. A., and Bauer, Herman E. II. Venous Pressure, a Simple Bedside Method, in *Collected Papers of the New York Homeopathic Medical College and Flower Hospital*, 1935, vol. 5, pp. 45-52. Goldbloom, A. Allen and Roht, P. K. III. Clinical Evaluation of Cardiac Output Studies, *Internat. Clin.* **3** 206, 1936.

4 Frothingham, Channing. A Case of Extensive Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Arteries, *Am. J. Path.* **5** 11, 1929.

5 A detailed pathologic study is to be reported elsewhere by Dr. Alfred Plaut, pathologist for the Beth Israel Hospital.

grayish white, round and oblong spots adhering to some cylindric structures corresponding to the obliterated vessels. Further incision revealed additional dark red thrombi.

Microscopic Postmortem Examination—The gray foci observed grossly proved to be completely obliterated blood vessels. In most cases the lumen was entirely filled with rather cellular fibrous tissue, with larger or smaller spaces of recanaliza-

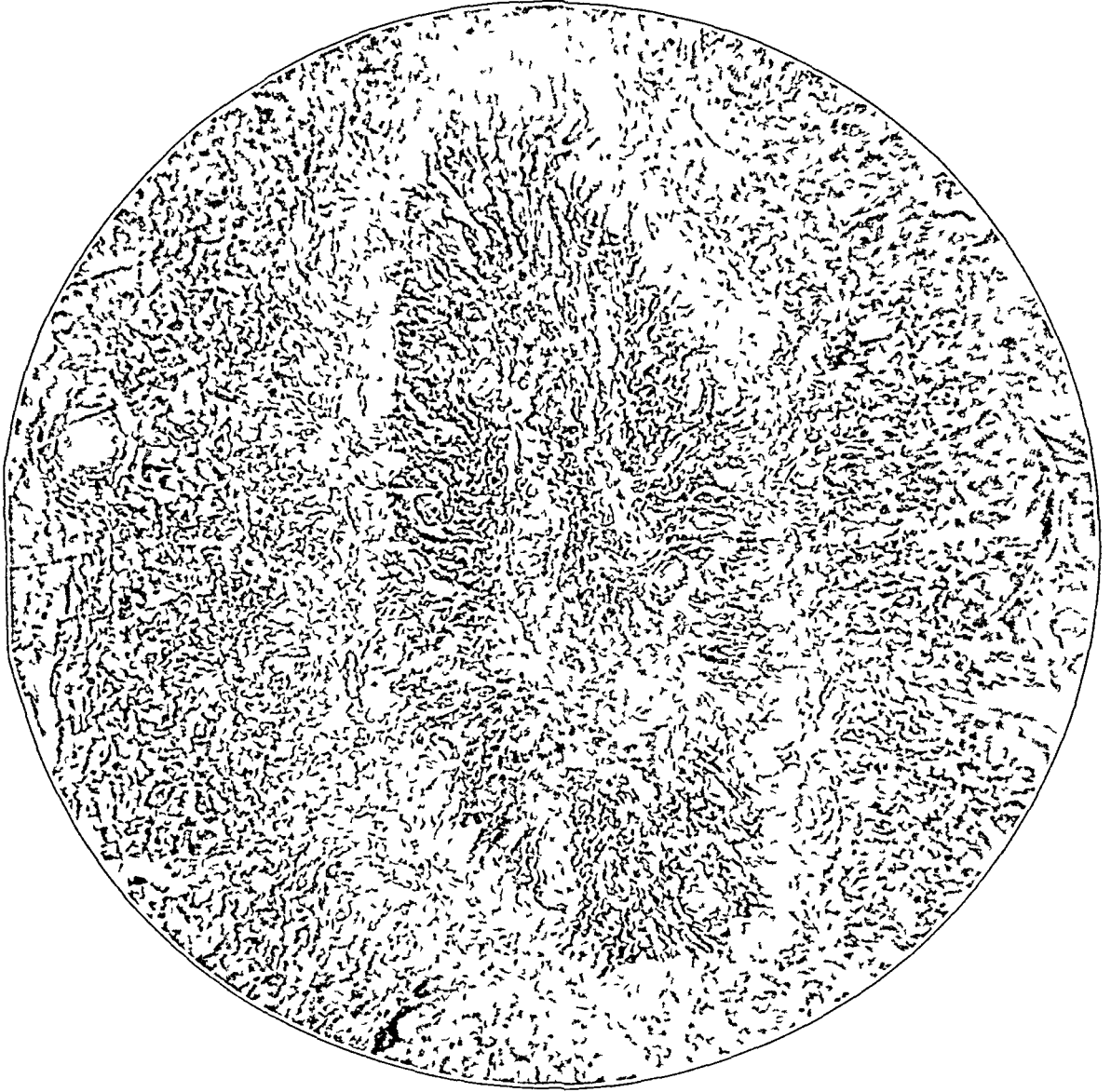


Fig 5—Microscopic section showing a completely fibrosed artery of the lung, with obliteration of the lumen, Van Gieson stain

tion. True inflammatory lesions were present in only a few places, represented by rather uncharacteristic granulation tissue, in which, however, giant cells were conspicuous. The thrombosed vessels observed grossly appeared to be intact. Some arteries showed an obviously inflammatory overgrowth of intima. In these vessels the intimal cells had large nuclei. Other arteries, again, had a small, regular intimal overgrowth without any evidence of inflammation. In a large number of obliterated arteries no remnants of thrombotic material were observed. The myocardium contained granulation tissue and scars (fig 5).

COMMENT

Eppinger and Wagner⁶ reported eight cases of primary arteriolar disease, with invasion of the small pulmonary vessels, producing circulatory failure. Careful analysis, however, reveals that in only two cases was there true obliterating arteritis. In the others there was primary vascular disease, with characteristics of either thrombo-angitis or obliterative sclerotic arteriolar disease.

Cases similar to the one herein described have been reported recently by Frothingham,⁴ MacCallum,⁷ and Waring and Black.⁸ The patient reported on by Frothingham was seen by one of us (Dr Rothschild). Pathologic examination showed that all the pulmonary arteriolar branches were completely occluded by thrombi, the smallest branches showing primary acute lesions and a condition simulating thrombo-angitis obliterans.

There is growing interest in the consideration of primary arterial disease, particularly notable being a series of articles recently published by Brenner.⁹

Circulatory failure of an extracardiac nature, due to pulmonary emphysema, kyphoscoliosis, Ayerza's disease¹⁰ or hypertension, or secondary to sclerosis of the larger arteries, is of frequent occurrence. Likewise, sclerosis of the pulmonary arterioles, with sclerosis of the pulmonary artery with or without general arteriosclerosis, is not uncommon as a cause of circulatory failure of extracardiac origin. Many years ago von Neusser called attention to the fact that in these cases there is marked dyspnea even on slight exertion, producing symptomatic polycythemia or cyanosis, giving cause for suspicion of sclerosis not only of the pulmonary artery but of the arterioles and capillaries as well, leading to fibrosis of the pulmonary alveoli and producing status volumen pulmonum auctum, with eventual failure of the right side of the heart. More recently, Moschcowitz¹⁰ and Miller¹¹ have shown that sclerosis of the pulmonary artery, with or without involvement of the smaller

6 Eppinger, Hans, and Wagner, R. Zur Pathologie der Lunge, Wien Arch f inn Med **1** 83, 1920.

7 MacCallum, W. G. Obliterative Pulmonary Arteriosclerosis, Bull Johns Hopkins Hosp **49** 37, 1931.

8 Waring, James J., and Black, W. C. Syndrome of Obstruction in Lesser Circulation, Am J M Sc **187** 652, 1934.

9 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation, Arch Int Med **56** 211 (Aug), 457 (Sept), 724 (Oct), 976 (Nov), 1189 (Dec) 1935.

10 Moschcowitz, Eli. The Cause of Arteriosclerosis, Am J M Sc **178** 224 (Aug) 1929.

11 Miller, H. R. Sclerosis of Pulmonary Artery and Its Branches, M Clin North America **9** 673 (Nov) 1925.

vessels, is not uncommon. The symptom complex which goes under the name *cor pulmonale* and which is due to the cause mentioned has long been recognized. However, obliterating arteritis of the small pulmonary vessels leading to cardiac failure (*cor pulmonale*) deserves emphasis because of its rarity.

In the few cases of localized obliterating arteritis reported in the literature the pulmonary lesion showed extensive fibrosis of the alveolar septums, many being almost avascular, with a peculiar peribronchial and perivascular increase in connective tissue. In addition, there were thrombosis and complete obliteration of the smaller arteries and in some cases infarction of the lungs.

As yet, the etiologic factor in obliterating arteritis of the pulmonary arterioles is undetermined. It is well known that infarction can cause arteritis or periarteritis nodosa and that the rheumatic virus has a marked affinity for the pulmonary vessels. But in the case reported herein there was no evidence of either a generalized or a rheumatic infection (the latter was ruled out by the absence of Aschoff bodies).

Judging from the onset of symptoms in the cases that have been reported and in our case, there is a possibility that allergy may play a role. This concept is based on the following supposition. Since it is known that all allergic manifestations, from the severest anaphylactic shock followed by death to chronic allergy, are characterized by spasm of the small arterioles and capillaries, it is possible that the first attack described by the patient, in which he suffered shortness of breath while walking and distress in the chest, may have been the initial manifestation of an allergic condition. As this continued, secondary changes in the lungs took place, followed eventually by dilatation of the right side of the heart, failure of the left ventricle, edema of the lungs and death.

From the clinical standpoint obliterating arteritis of the pulmonary arterioles might well be divided into three stages.

1. The immediate anaphylactic stage is of short duration and is characterized by an abundance of symptomatic complaints and a minimum of objective findings. Discomfort in the chest and tachypnea are noted but no dyspnea and only moderate tachycardia.

2. The allergic stage is characterized by spasm of the pulmonary arterioles, accompanied with marked subjective symptoms, as the vascular changes lead to secondary changes in the lungs, moderate dyspnea, slight cyanosis and marked tachycardia are also present. There is evidence of localized fibrosis, pneumonitis and pleuritis. The involved lung shows diminished aeration and restricted mobility of the affected side and of the corresponding diaphragmatic excursion. There is likewise evidence of obstruction of the lesser circulation, in that there are an accentuated pulmonic second sound and a split first sound. The night

ventricle becomes enlarged, and there is electrocardiographic evidence of myocardial damage. The most valuable diagnostic aid is the finding of diminished oxygen saturation of the arterial blood.

3. The terminal stage is characterized by failure of the right ventricle, giving rise to relative tricuspid insufficiency, enlargement of the liver and eventual failure of the left ventricle, with edema of the lungs.

CONCLUSION

There may be localized obliterating pulmonary arteritis without involvement of the other vessels, constituting a distinct clinical entity.

A case is reported in which this condition was diagnosed ante mortem and confirmed at autopsy.

Obliterating arteritis is differentiated from thrombo-angitis obliterans in that the former is confined to the smallest arterioles without affecting the venous system.

The theory is advanced that the initial cause of the disease in our case was of an allergic nature. The condition began with anaphylactic shock, causing primary tachypnea with no dyspnea and resulting in interference with the pulmonary circulation. As the cause was not removed, there ensued secondary changes in the arterioles leading to obliterating arteritis, with consequent pathologic changes in the lungs. The right side of the heart became dilated as a result of enlargement of the right ventricle, producing anoxemia and abnormal electrocardiographic findings. Finally the left ventricle, which could not receive a sufficient amount of blood, dilated, and there followed ventricular failure and pulmonary edema.

The clinical course of circulatory failure in our case bears a striking resemblance to the circulatory failure secondary to bronchial asthma with permanent changes in the lungs, producing cardiac failure from overtaxation of the right side of the heart.

The finding of diminished oxygen saturation of the arterial blood is of diagnostic significance. Also indicative of pulmonary arterial obstruction, particularly in young persons, are cyanosis, tachypnea, with no orthopnea, and tachycardia.

This condition may be divided into three stages: the immediate anaphylactic, the allergic and the terminal stage, with circulatory failure.

Dr. I. W. Held was of aid in an advisory capacity, Dr. Alfred Plaut reported on the pathologic specimens and Dr. Ella Fishberg carried out the detailed work on the association curves.

RENAL INSUFFICIENCY FROM BLOOD TRANSFUSION

II ANATOMIC CHANGES IN MAN COMPARED WITH THOSE IN DOGS WITH EXPERIMENTAL HEMOGLOBINURIA

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The transfusion of incompatible blood into man is accompanied with or immediately followed by chills, fever, nausea and vomiting, acute pains in the muscles, dyspnea and a feeling of constriction in the chest. Signs of hemolysis *in vivo* may occur within a few hours. These include hemoglobinemia, hemoglobinuria and jaundice. If a relatively small amount of blood is hemolyzed, hemoglobinuria and jaundice may not be evident. Drabkin¹ has shown that only about 10 per cent of the hemoglobin that disappears from the blood stream of the dog appears in the urine. The patient may recover with nothing more serious than the loss of the transfused erythrocytes and consequent hemoglobinuria for several days. In some cases, however, the sequelae are more grave. The urinary excretion is immediately diminished, or ceases entirely and the products of nitrogen metabolism increase rapidly in the blood. Vomiting continues, and generalized edema sometimes appears. Coma gradually supervenes, sometimes with convulsions and the patient dies with the usual signs of uremia. Hypertension is usually absent. The picture may be complicated by subserous and subcutaneous hemorrhages. Death usually occurs from four to twelve days after the transfusion. At any time after the transfusion spontaneous diuresis may occur and recovery may take place. This probably happens in only a minority of the cases.

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1 Drabkin, D. L., Widerman, A. H. and Landow, H. Fate of Hemoglobin Injected into the Blood Stream. *J. Biol. Chem.* **109** 222-223 (May) 1935.

A similar syndrome has been noted in blackwater fever and in hemoglobinuria due to quinine²

In 1931 Bordley³ reviewed the literature and discussed four theories which might explain the renal lesions resulting from reactions to blood transfusion. 1 The theory of mechanical blockage of the renal tubules was first proposed by Yorke and Nauss⁴ and later amplified and defined by Baker and Dodds⁵. In its present form, as elaborated by the experiments of the latter authors, it attempts to account for the renal insufficiency by the precipitation of hemoglobin in the renal tubules when that pigment makes contact with urine which is acid in reaction. The hemoglobin is excreted in solution when the urine is alkaline. The operation of this mechanism was conclusively demonstrated by Baker and Dodds in rabbits. 2 The theory of anaphylaxis was derived from some observations made by Longcope and Rackemann⁶ that in patients with urticaria, renal insufficiency developed coincidentally. DeGowin, Osterhagen and Andersch,⁷ however, have produced the syndrome in dogs with a single transfusion of canine hemoglobin. 3 The theory that renal damage is in some way a result of the hypochloremia due to vomiting was advanced on the basis of the clinical studies on high intestinal obstruction by Brown, Eusterman, Hartman and Rowntree⁸. Some of their patients died of renal insufficiency and proved to have necrosis of the tubular epithelium. Chemical studies of the blood of patients with transfusion anuria have shown that the plasma chlorides are depleted only after renal insufficiency has developed. 4 The explanation that a nephrotoxic substance is released from the hemolysis of blood seems to coincide with the acute nephrotic type of lesion seen in some of the human cases. No experimental proof has been advanced for this theory. To these four theories the independent investigations

2 Terplan, K. L., and Javert, C. T. Fatal Hemoglobinuria with Uremia from Quinine in Early Pregnancy, *J. A. M. A.* **106** 529-532 (Feb. 15) 1936.

3 Bordley, J., III. Reactions Following Transfusion of Blood with Urinary Suppression and Uremia, *Arch. Int. Med.* **47** 288-315 (Feb.) 1931.

4 Yorke, W., and Nauss, R. W. The Mechanism of the Production of Suppression of Urine in Blackwater Fever, *Ann. Trop. Med.* **5** 287-312, 1911.

5 Baker, S. L., and Dodds, E. C. Obstruction of the Renal Tubules During the Excretion of Hemoglobin, *Brit. J. Exper. Path.* **6** 247-260 (Oct.) 1925.

6 Longcope, W. T., and Rackemann, F. M. Renal Insufficiency with Urticaria, *J. Urol.* **1** 351-366 (Aug.) 1917.

7 DeGowin, E. L., Osterhagen, H. F., and Andersch, M. Renal Insufficiency from Blood Transfusion. I. Relation to Urinary Acidity, *Arch. Int. Med.* **59** 432-444 (March) 1937.

8 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* **32** 425-455 (Sept.) 1923.

of Mason and Mann,⁹ in the United States, and Hesse and Filatov,¹⁰ in Russia, have added another alternative explanation. They have shown that the intravenous injection of hemoglobin produces a diminution in the volume of the kidney by vasoconstriction. The Russian writers have stated the opinion that the renal insufficiency is on the basis of ischemia of the kidneys. The experiments of Mason and Mann have shown that the vasoconstriction is only a transitory phenomenon, and it is difficult to reconcile this theory with the anatomic lesions seen in human kidneys.

It seems that histologic studies of the kidneys of patients dying of transfusion anemia should definitely confirm or disprove the theory of pigment obstruction of the renal tubules. In reading the literature, however, one finds no consensus regarding the cause of the renal insufficiency. Practically all writers describe some necrosis of the renal epithelium and the presence of some hemoglobin pigment, but the extent of these changes varies considerably in different cases. Whereas one patient shows extensive epithelial damage and little pigment, another may show little necrosis and much precipitated hemoglobin. Because of the scarcity of cases, no one writer has had the opportunity to study more than two or three. Still fewer observers have been able to compare human tissues with those of experimental animals. As a result, some writers support the theory of mechanical obstruction, and others with an equal amount of experience but with dissimilar cases are proponents of a nephrotoxic reaction.

MATERIAL AND METHOD

We have had the opportunity of making an examination of the tissues of five patients from our own autopsy service and those of two patients from the autopsy service of Dr. E. T. Bell, professor of pathology at the University of Minnesota. Single specimens were lent to us by Dr. M. F. Hassett, of St. Paul, Dr. M. L. Weinstein, of Chicago, and Dr. A. M. Moody, of San Francisco. In addition, the renal sections of a woman dying of hemoglobinuria due to quinine were lent to us by Dr. K. L. Terplan, of Buffalo. The latter case was reported by Drs. Terplan and Javert.² Our own experiments on dogs have provided an abundance of pathologic material for comparison. The details of these experiments have already been published.⁷ Dogs were fed with beef and ammonium chloride so that the urine was acid in reaction. They were then given transfusions of solution of canine hemoglobin. This resulted in death in uremia in four to ten days. This syndrome did not occur in dogs which were given transfusions when the urinary reaction was alkaline.

⁹ Mason, J. B., and Mann, F. C. Effect of Hemoglobin on Volume of the Kidney, *Am J Physiol* **98** 181-185 (Sept.) 1931.

¹⁰ Hesse, E., and Filatov, A. Experimentelle Untersuchungen über das Wesen des hämolytischen Shocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben, I. Die Nierenfunktionsstörungen im akuten Experiment, *Ztschr f d ges exper Med* **86** 211-230 1933. Iljin, W. Experimentelle Beobachtungen der Nierentätigkeit nach Einführung von heterogenem und autohämolyisiertem Blut, *Arch f klin Chir* **181** 240-249, 1934.

TABLE 1—Summary of Anatomic Data for Dogs Dying of Causes Other Than Uremia

Dog No	Urinary Reaction	Cause of Death	Number of Transfusions	Days Lived After Transfusion	Maximum Blood Urea Nitrogen, Mg per 100 Cc			Kidneys				interpretation
					Liver Necrosis	Liver Hemosiderin		Tubular Dilatation	Element and Crystals	Regeneration of Tubular Epithelium		
6	Alkaline	Killed	14	8	11.9	0	+++	+++	0	0	0	Normal except for hemosiderosis
4	Alkaline	Killed	9	50	46.9	0	+++	+++	0	0	0	Normal except for hemosiderosis
7	Acid	Speed shock	2	0	25.0	0	++	+	++	0	0	Normal except for hemosiderosis
9	Acid	Pneumonia	2	1	47.6	0	++	+	0	+	0	Normal except for hemosiderosis
13	Alkaline	Toxic blood	8	0	50.1	0	+++	++	0	0	0	Normal except for hemosiderosis
14	Acid	Pneumonia	2	1	15.0	0	+	+	0	0	0	Normal except for hemosiderosis
15	Acid	Toxic blood	1	0	23.1	0	+	+	++	+	0	Slight pigment obstruction
16	Acid	Toxic blood	3	0	30.8	0	++	+	+	+	0	Slight pigment obstruction
19	Acid	Speed shock	1	0	91.5	0	0	0	0	0	0	Normal

MORBID ANATOMY OF DOGS WITH HEMOGLOBINURIA

Our pathologic studies included the postmortem examination of the tissues of twenty-four dogs which had received from one to fourteen transfusions of hemolyzed erythrocytes from other dogs. The interval between transfusions was never less than one week. The average dose was 10 cc of packed erythrocytes per kilogram of body weight. The blood was defibrinated, and the corpuscles were separated from the serum by centrifugation and were hemolyzed by the addition of distilled water in the proportion of 3 volumes of cells to 4 volumes of water. Dogs were selected which appeared healthy and whose urine was consistently free from albumin. These precautions proved to be adequate so that little evidence of chronic nephritis was observed at autopsy and no lesions were encountered which confused the anatomic picture in which we were interested.

At each transfusion the dose of solution of hemoglobin was sufficient to produce gross hemoglobinuria for two or three days. Chemical tests for hemoglobin in the urine gave positive results for approximately two more days. Casts of pigment never appeared in the urine except when there was retention of nitrogen in the blood.

Deposition of Hemoglobin Pigment in the Tissues (figs 1 and 2) — With each transfusion there was a deposition of hemosiderin in the tissues. This occurred in all dogs whether or not death had occurred from renal insufficiency. The amount of hemosiderin was roughly proportional to the number of transfusions received. With relatively few transfusions, granules of pigment could be seen in the renal epithelium and in the Kupffer cells of the liver. The granules were small, and in sections stained with hematoxylin and eosin they appeared golden yellow. They gave the iron reaction with potassium ferriocyanide stains. In the kidney the cells of the proximal convoluted tubules contained large amounts of similar pigment. Occasionally some pigment could be seen in the cells of other portions of the renal tubules, even in the collecting tubules. When larger amounts of hemoglobin had been injected, hemosiderin was accumulated in the stroma near the capsule and along radial lines projecting into the cortex.

In the liver the hemosiderin was present in the Kupffer cells. When repeated injections of hemoglobin had been given dense pigment masses were also aggregated in discrete foci of large mononuclear cells scattered throughout the hepatic substance.

The reticulo-endothelial cells of the spleen and lymph nodes also contained deposits of hemosiderin.

Anatomic Picture in Dogs with Alkaline Urine (figs 1, 2 and 7 and table 1) — Dogs 3 and 4 were killed after fourteen and nine transfusions respectively. The tissues were entirely normal except for the deposits of hemosiderin previously described. Dog 12 received a similar alkaline

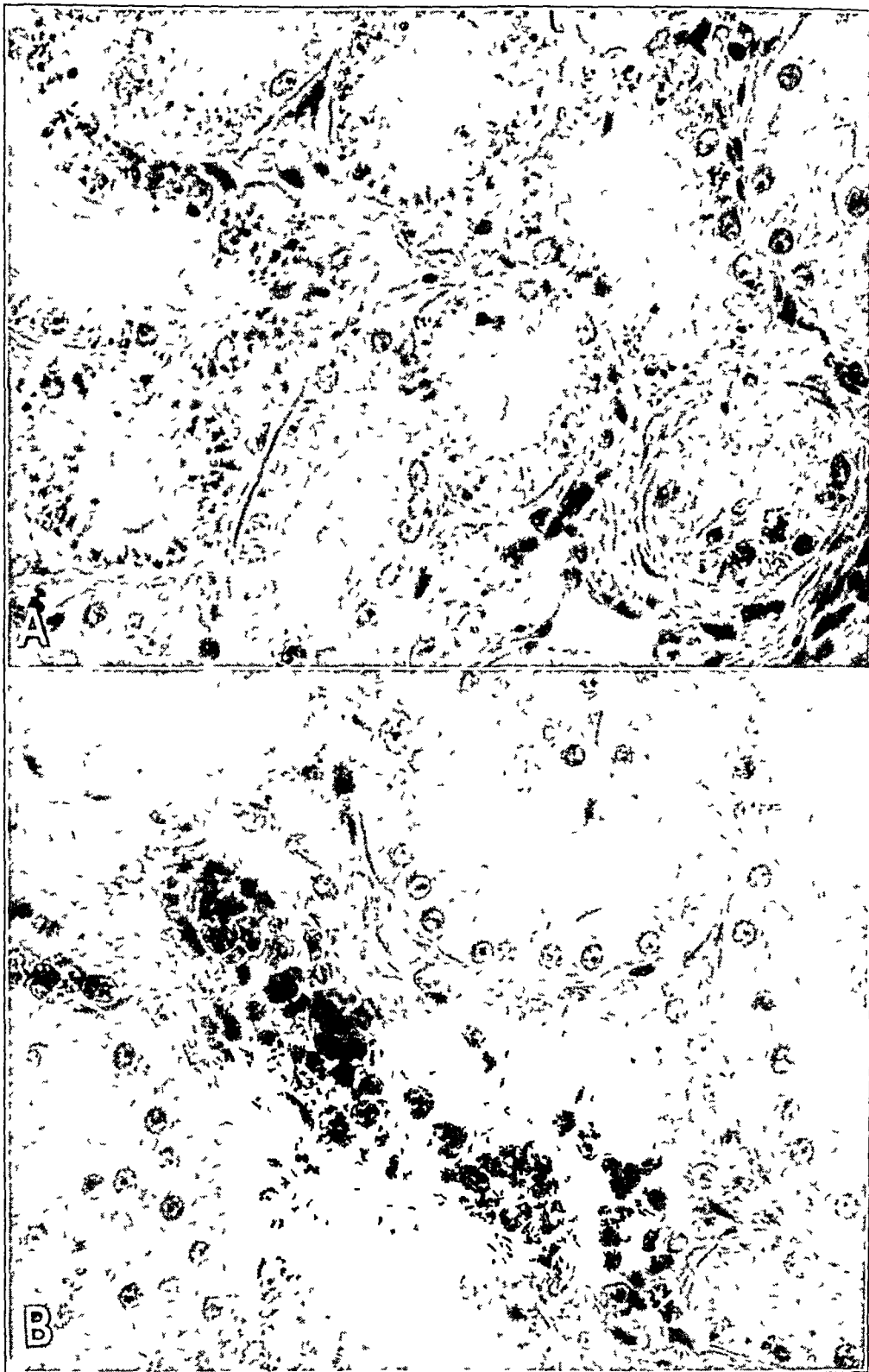


Fig 1—Deposition of hemosiderin *A*, renal convoluted tubules, showing the epithelial cells containing granules of hemosiderin (photographed as black dots) Photomicrograph of tissue from dog 4 which was killed after receiving nine transfusions of hemoglobin when the urine was alkaline *B*, an island in the renal stroma composed of masses of hemosiderin granules and large mononuclear cells (dog 4)

diet but at times refused to eat and on those occasions the urine became acid. When a transfusion was given while the urine was alkaline no retention of nitrogen developed, if it was given when the urine was acid various degrees of azotemia were induced. The animal was killed when recovering from one episode of uremia, and the kidneys showed the typical nephropathic picture to be described in association with dogs with acid urine. Dog 13 was killed inadvertently with solution of

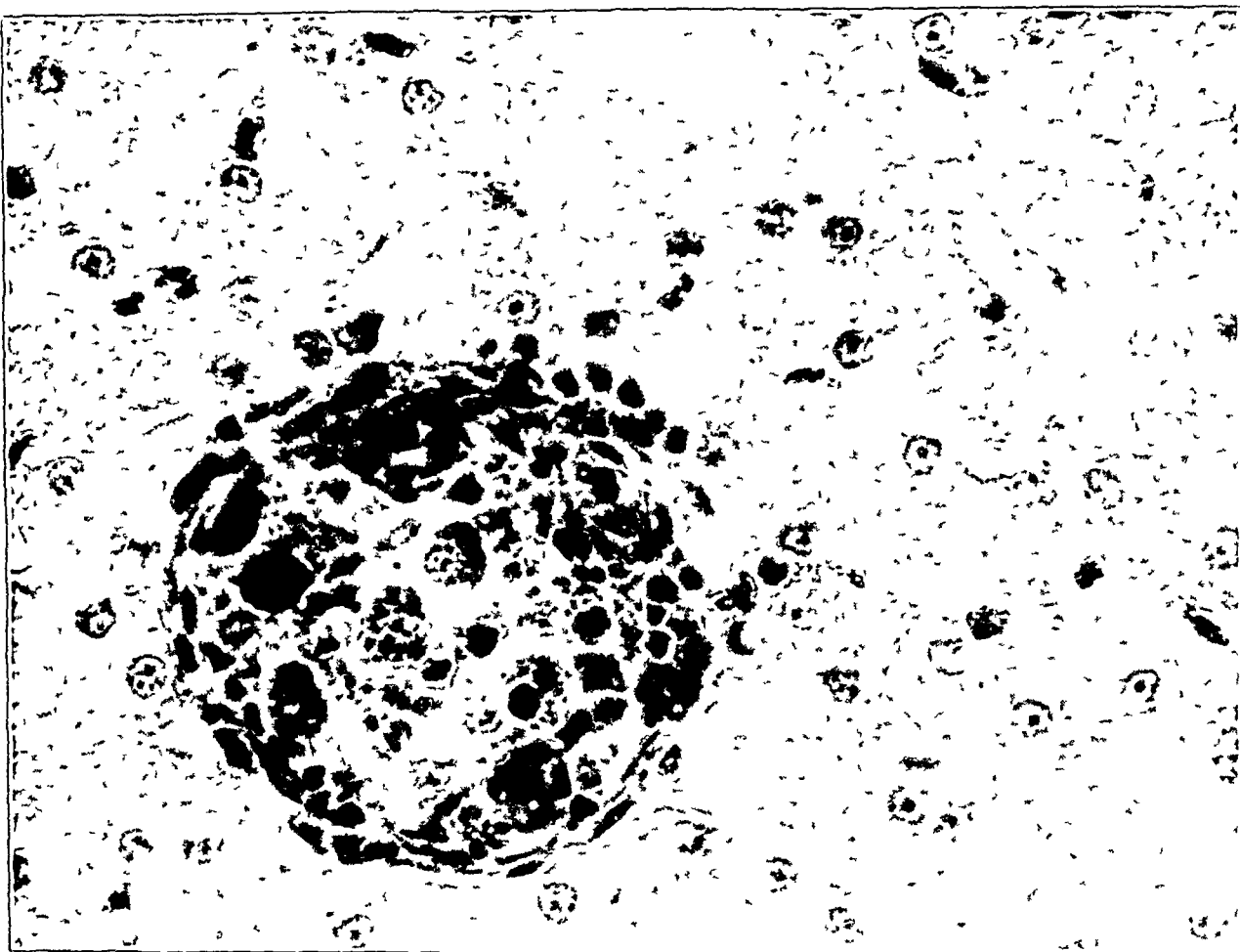


Fig 2—Deposition of hemosiderin. Section of liver, showing several isolated cells of Kupffer containing granules of hemosiderin and a large island of hemosiderin granules and mononuclear cells in the parenchyma (dog 4)

hemoglobin which was grossly contaminated with bacteria and which proved highly toxic for all four dogs to which it was given. The liver and kidneys however, except for some hemosiderosis were entirely normal.

Anatomic Picture in Dogs with Acid Urine (figs 3 to 10 and table 2)—Six dogs with acid urine died from causes other than uremia. Two died of "speed shock" (dogs 7 and 19), two died of bronchopneumonia

TABLE 2—Summary of Anatomic Data for Dogs Dying of Uremia

Dog No	Urinary Reaction	Cause of Death	Number of Trans fusions	Days Lived After Trans fusion	Maximum		Kidneys						Interpretation	
					Blood Urea Nitrogen, Mg per 100 Cc	Necrosis	Liver		Hemo siderin	Tubular Dilata tion	Pigment Casts and Crystals	Regenera tion of Tubular Epithe lium		
							Hemo siderin	Hemo siderin						
1	Acid	Uremia	4	10	119.0	0	++++	++++	++++	+	+++	++	+	Pigment obstruction
2	Acid	Uremia	2	9	217.7	++	++++	++++	++++	++++	++	++	++	Pigment obstruction
5	Acid	Uremia	3	8	217.7	0	++++	++++	++++	++++	++	+	+	Pigment obstruction
11	Acid	Uremia	2	4	350.0	+	+	0	++++	++++	++++	++++	++++	Pigment obstruction and necrosis
12	Acid	Killed (recovering from uremia)	10	9	133.9 123.0*	0	++	++	++	++	++	+	++	Pigment obstruction
20	Acid	Killed (recovering from uremia)	1	5	119.0 95.6*	0	+	+	+	++	+	+	++	Pigment obstruction
21	Acid	Uremia	1	1	266.7	0	+++	+	+	+	+++	+++	++	Pigment obstruction and necrosis
23	Acid	Uremia	1	7	924.1	0	+	+	+	+	+	++	0	Tubular necrosis
24	Acid	Uremia	1	7	362.6	0	++++	+	+	++	++++	++	+++	Pigment obstruction

* The value at the time the dog was killed

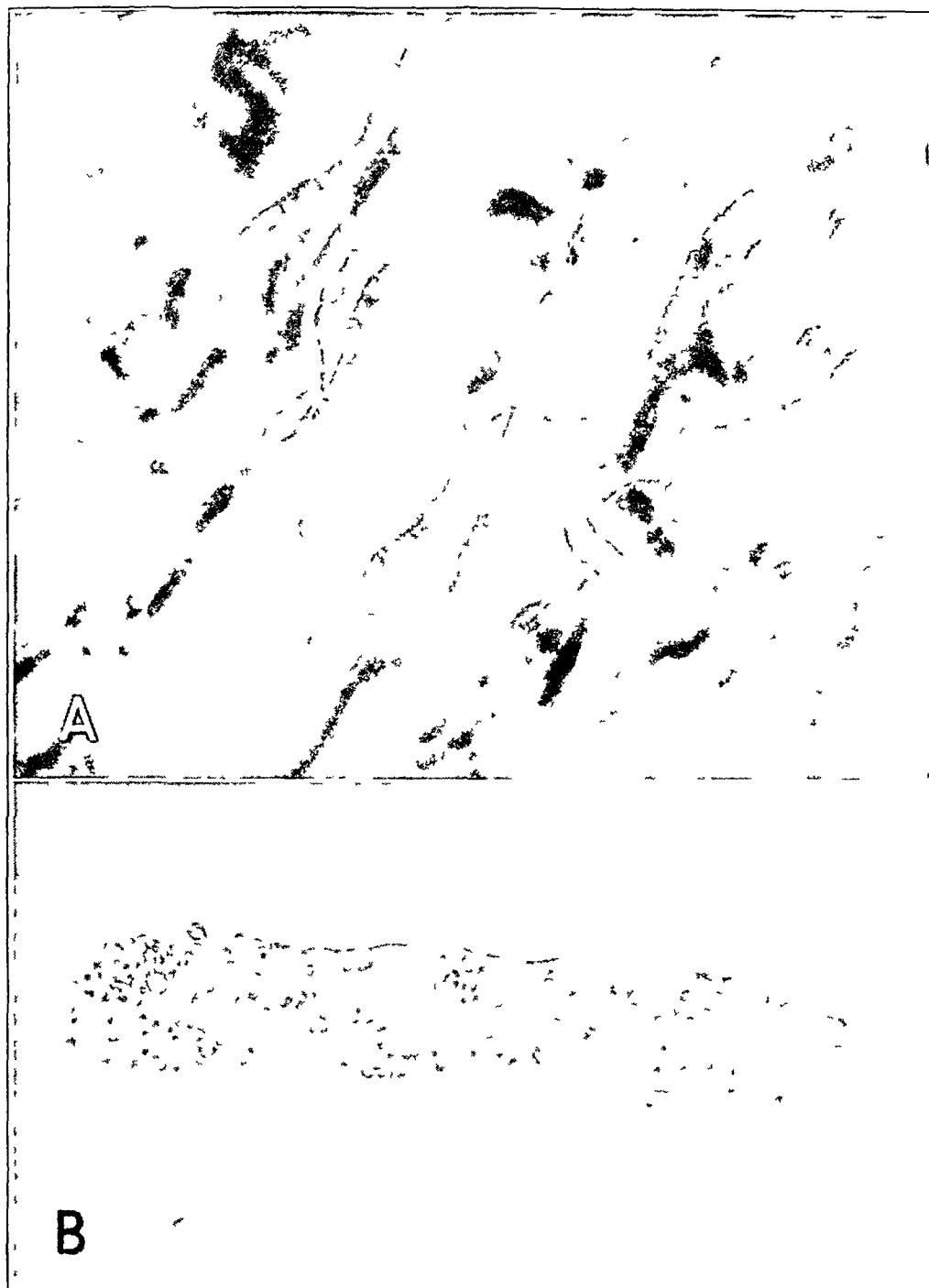


Fig 3—Tubular obstruction *A*, unfixed and unstained section of kidney, photographed one hour post mortem, showing tubular lumens outlined by brown pigment casts. Several loops of Henle are shown. Section from the kidney of dog 21, which died of uremia four days after a single transfusion received when the urine was acid. *B*, a single pigment cast teased from the preparation pictured in *A*. The cast was brown and opaque and when viewed through the microscope seemed composed of small masses of pigment molded together.

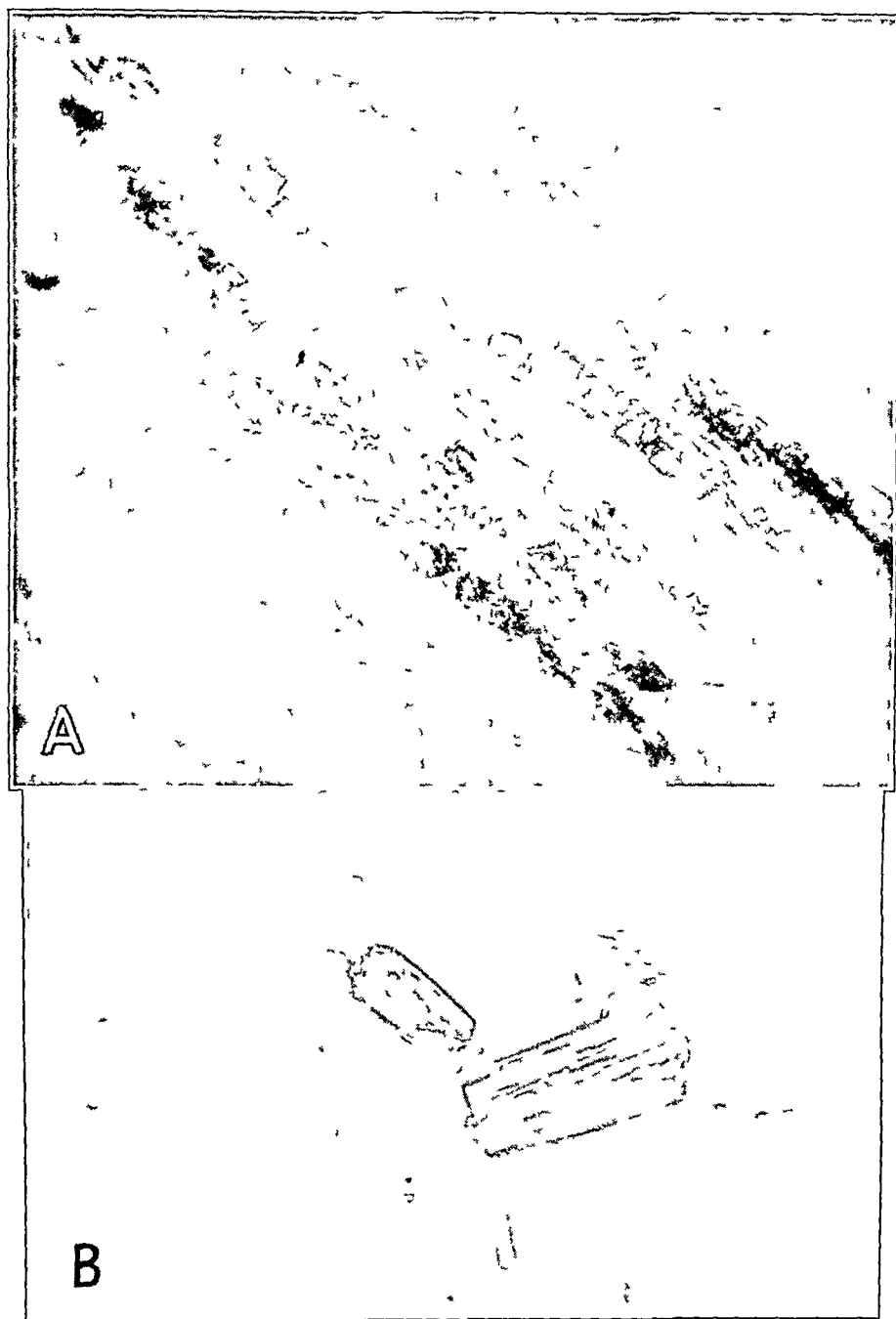


FIG 4—Tubular obstruction *A*, tubular lumens filled with brown crystals of pigment This is in the medullary region of the same preparation depicted in figure 3 *A* *B*, two brown crystals teased from the preparation pictured in *A* The form of the crystals resembles that of canine hemoglobin

(dogs 9 and 14) and two died because the solution of hemoglobin was contaminated (dogs 15 and 16). In none of these were there significant lesions of the kidneys or liver except for the hemosiderosis common to all dogs receiving solution of hemoglobin. In dogs 15 and 16 there were, however, a few pigment casts, indicating an early stage of obstruction. This group served as controls to show that the diet of beef and ammonium chloride produced no renal damage.

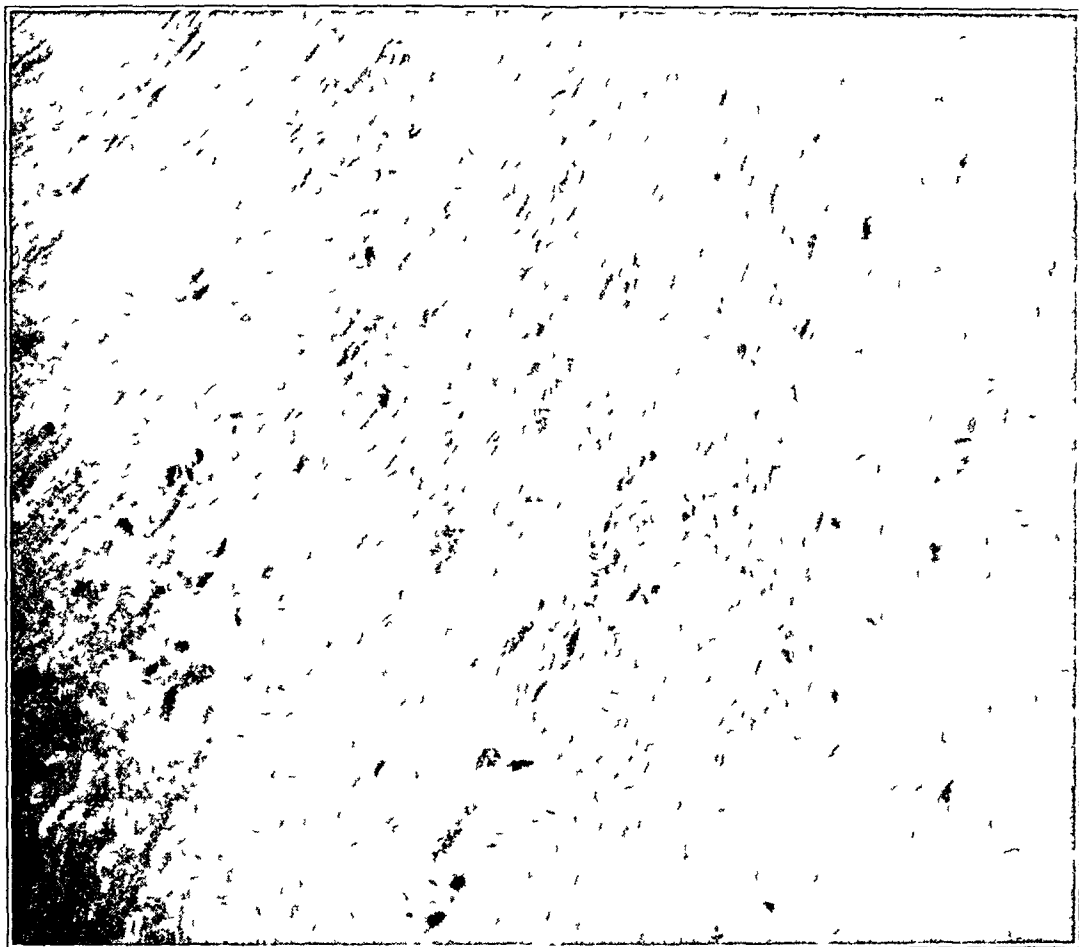


Fig 5—Tubular obstruction. Pigment casts were formed in the region of the corticomedullary junction and followed the cortical rays toward the periphery. Peripherally from this zone of casts, the lumens were dilated. Low magnification of a fixed and stained sagittal section from the kidney of dog 2, which died in uremia nine days after receiving a transfusion when the urine was acid.

Seven dogs (dogs 1, 2, 5, 11, 21, 23 and 24) died in uremia and two (dogs 12 and 20) were killed when recovering from episodes of azotemia. The livers of dogs 2 and 11 contained some necrosis about the central veins of the lobules. In all other dogs of both groups the livers were essentially normal except for the hemosiderosis previously described.

The kidneys of the dogs dying of renal insufficiency showed striking pictures. They were slightly increased in size. The capsules were not adherent. Fresh sections revealed a dark reddish brown zone marking the corticomedullary junction, with radial projections of the same color extending into the cortex. When thin slices of fresh kidney were examined with a dissecting microscope by transmitted light, Henle's loops, the recurring limbs and the collecting tubules were seen to

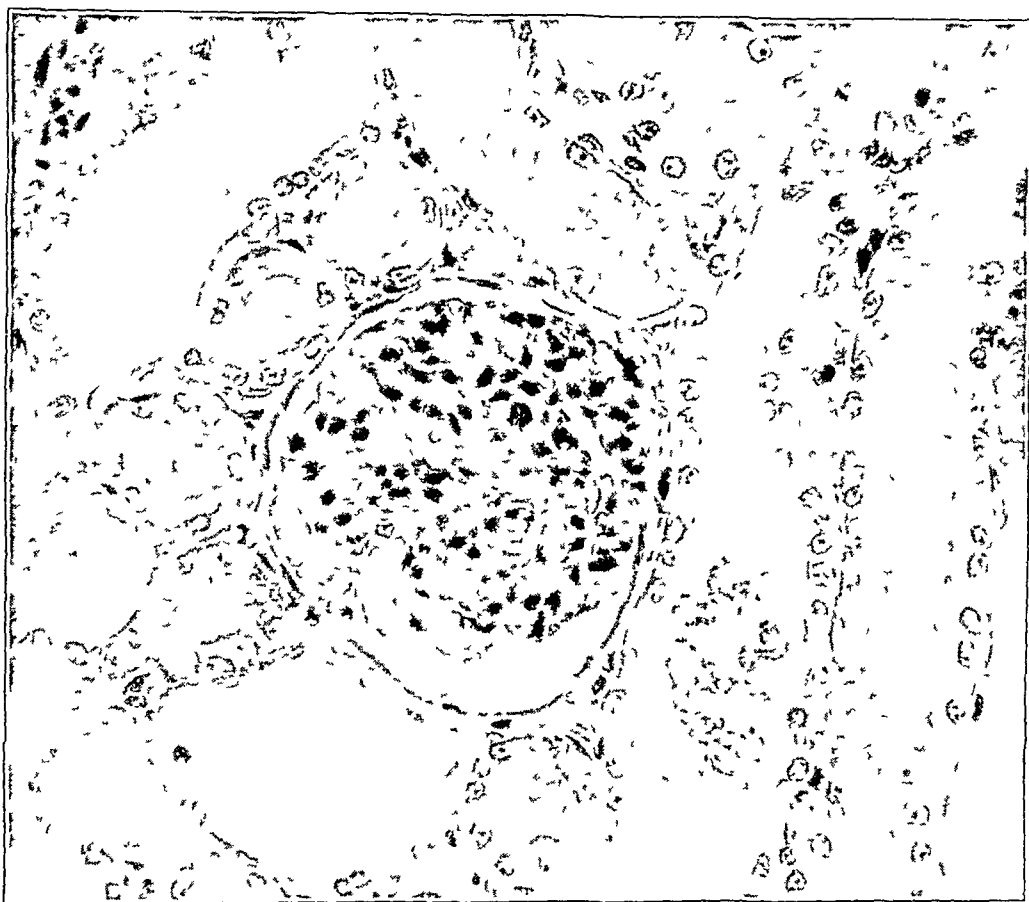


Fig 6—Tubular obstruction. This illustration depicts a normal glomerulus and moderate dilatation of the lumens of the convoluted tubules (dog 2)

be filled with a dark brown substance. In some areas brown crystals could clearly be seen in the lumens of the tubules. The crystals belonged to the monoclinic system. With teasing needles some of the casts and crystals were dislodged and photographed. This proved conclusively that the brown of the pigment casts was natural and that the crystals were not artefacts produced by staining and fixation. It has so far proved impracticable to separate enough material for spectroscopic and chemical analysis.

The kidneys were fixed in Zenker's solution and stained with hematoxylin and eosin. When appropriate sections were studied under low magnification, a broad zone could be seen in the region of the cortico-medullary junction. This area was remarkable because of the large numbers of pigment casts and crystals in the tubular lumens. The cortical rays also were made prominent because they were filled with the same substances.

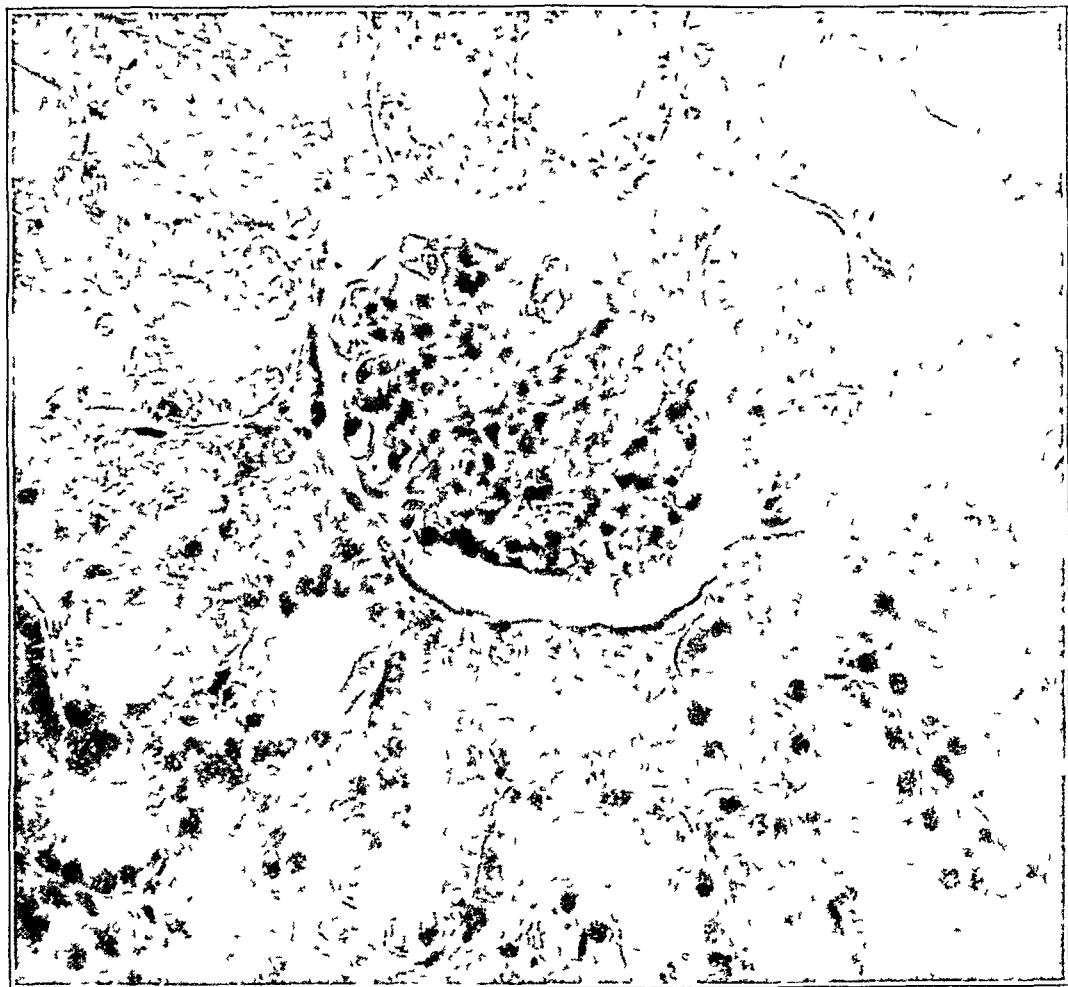


Fig 7—Normal dog kidney (to be compared with figure 6). A normal glomerulus with undilated tubules. The tubular epithelium contains granules of hemosiderin. Photomicrograph of section of tissue from dog 3, which was killed after fourteen transfusions, given when the urine was alkaline.

With higher magnification the glomeruli appeared normal. The crystals and casts occurred chiefly in the lumens of Henle's loops and of the recurring limbs and to a lesser extent in the collecting tubules. Proximal to these obstructions, the lumens of the descending limbs and the spaces of Bowman were dilated. The pigment masses and crystals appeared greenish brown. This was in contrast to the brownishness seen in the fresh, unfixed and unstained preparations. The green tint was probably caused by the action of the fixative on the pigment. The

greenish brown was also in contrast to the golden yellow of the hemosiderin contained in the epithelial cells. This suggests the inference that the pigment casts and crystals are not hemosiderin. This is supported by the fact that they did not give the prussian blue reaction. A few lumens were filled with polymorphonuclear leukocytes. Patchy areas of stroma were infiltrated with leukocytes. Special stains, however, never revealed the presence of bacteria.

Adjacent to the pigment casts and crystals there was some degeneration of epithelium. This was not marked. However occasional necrotic



Fig 8—Tubular obstruction. Tubular lumens in the region of Henle's loops were filled with greenish brown crystals of pigment, casts of amorphous pigment and some leukocytes. This section is from the same kidney as the section pictured in figure 5.

cells occurred in tubules which did not contain casts, and careful search usually revealed mitotic figures as evidence of regeneration. In some places tubules were lined with low cuboidal epithelium which could be interpreted either as regenerating epithelium or as residua after sloughing of portions of the cells.

In most of the kidneys studied the amount of necrosis was minimal. The essential lesion appeared to be simple mechanical blockage of the

tubules with pigment casts and crystals. The evidence of epithelial injury was marked in one dog (dog 21). In this animal, in addition to extensive obstruction, there was an extreme degree of necrosis of the cells of the convoluted tubules and deposition of calcium salts in some of the necrotic cellular debris.

From the histologic changes observed it was evident that two distinct and apparently separate pathologic processes were involved. The most common and striking one was that of tubular obstruction by pigment

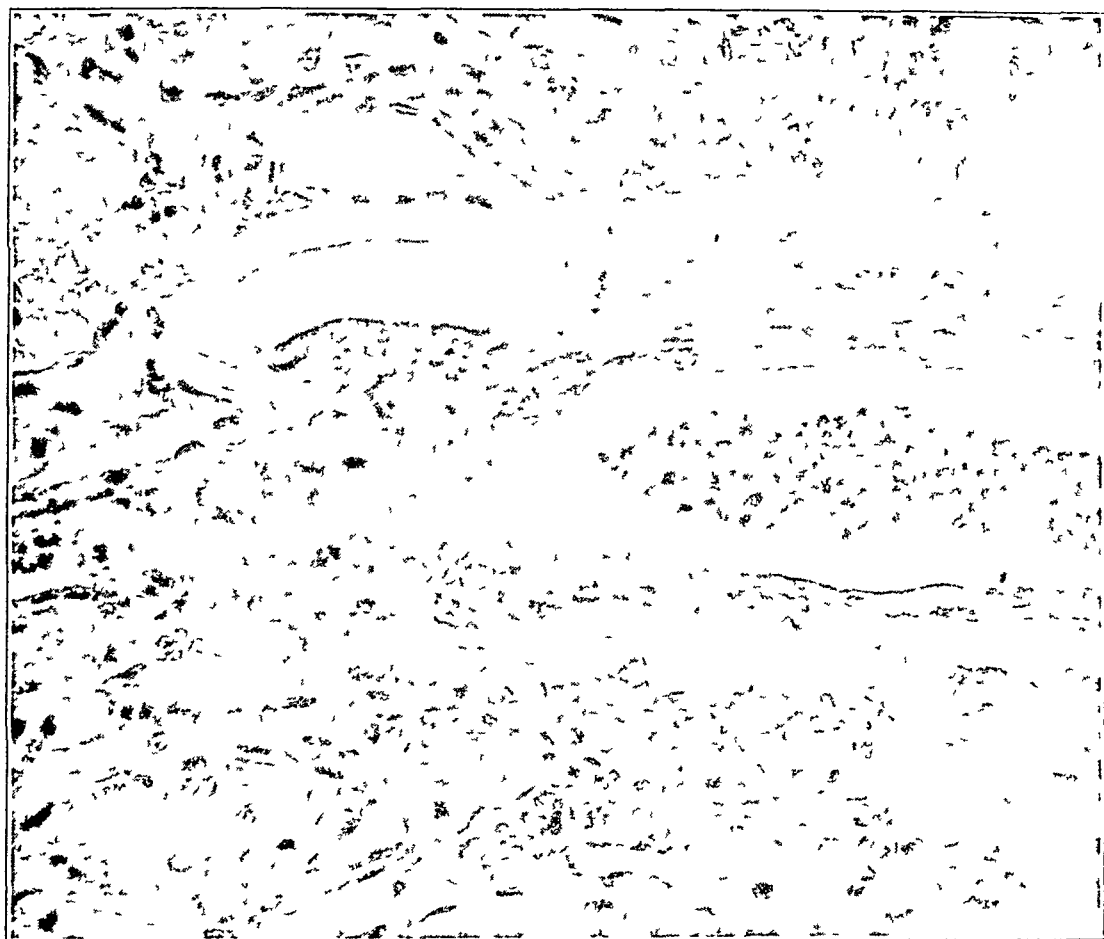


Fig 9—Tubular obstruction. Collecting tubules filled with leukocytes and pink-staining albuminous material. This section is from the same kidney as the section depicted in figure 5.

precipitated in the region of Henle's loops. The other was a destructive process involving particularly the epithelium of the convoluted tubules. The kidneys of dogs 1, 2, 5, 12, 20 and 24 showed the obstructive process in marked predominance. Dogs 21 and 11 showed a combination of extensive necrosis and marked obstruction with pigment. There was no significant obstruction in the kidneys of dog 23 and the amount of necrosis was not as extensive as that in dogs 21 and 11. No

correlation could be made between the occurrence of the type of lesion and any other factor. Neither the period of survival after transfusion nor the amount of retention of nitrogen seemed to have a direct relation. Many mitotic figures were seen in kidneys of animals which lived only four days after transfusion.

The most striking demonstration of the two types of renal lesions was obtained by study of dogs 23 and 24. These two animals both had acid urine, and the transfusions were given within the same hour with the same lot of solution of hemoglobin. The clinical courses were

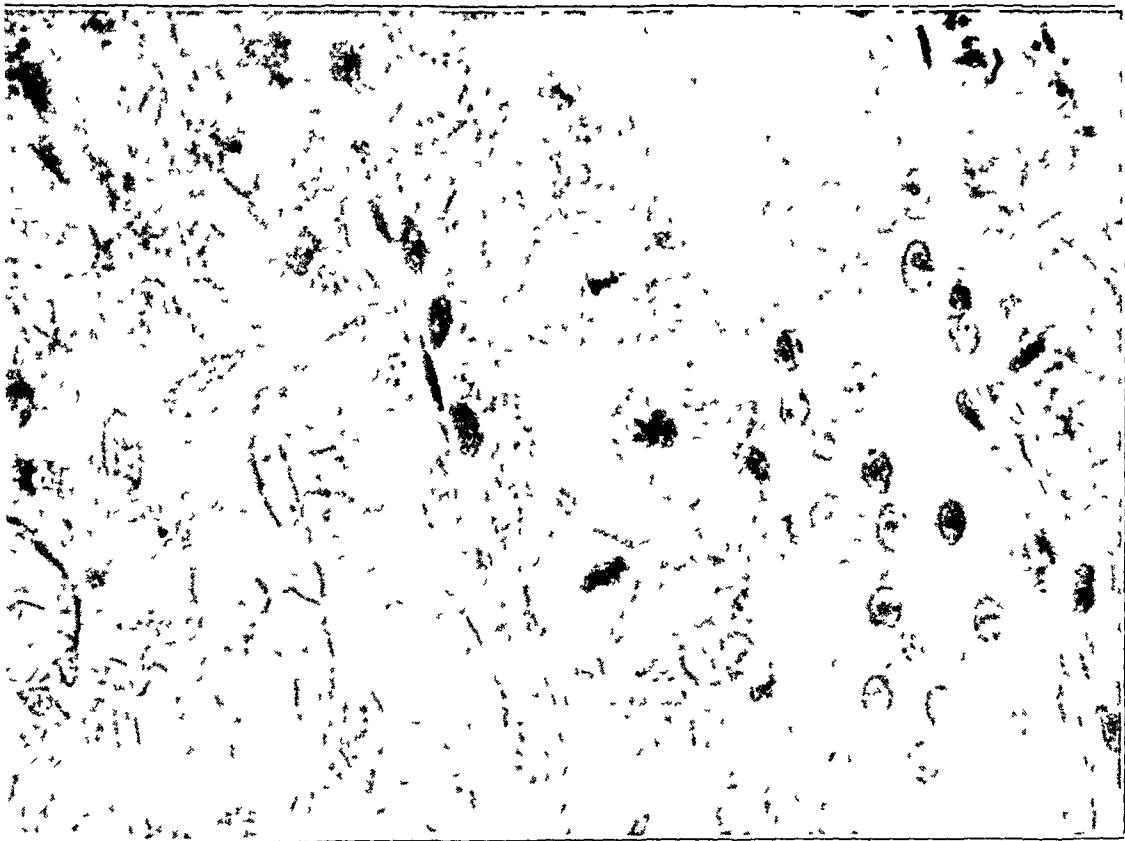


Fig 10—Tubular regeneration. Three mitotic figures are shown in the cross-section of a single convoluted tubule. In most kidneys, however, evidence of regeneration was not as common as is depicted here. Photomicrograph of a section of tissue from dog 24, which died in uremia seven days after a single transfusion received when the urine was acid.

unusually similar, both animals dying in coma seven days after the transfusion, with urea nitrogen values of 324.1 and 362.6 mg per hundred cubic centimeters of blood, respectively. The kidneys of dog 23 showed moderate necrosis and practically no obstruction with pigment, but the kidneys of dog 24 contained extensive obstructive lesions and a minimal amount of necrosis.

MORBID ANATOMIC PICTURE IN PATIENTS WITH POST-TRANSFUSION UREMIA (TABLE 3)

Studies were made of the kidneys of eight patients who died of renal insufficiency following blood transfusion and of one patient who died of uremia following hemolysis from quinine. Five patients with transfusion reactions were from our own autopsy service, and microscopic sections of the remaining four were lent to us by others. The kidneys of our patients were somewhat enlarged and congested. On section, brownish radial streaks could often be made out in the medulla. Microscopically, the anatomic basis for the renal insufficiency was not evident in the majority of the cases studied. Perhaps the most constant abnormality was edema of the interstitial tissues. A variable number of brown pigment casts were observed in the tubules, especially in Henle's loops and in the collecting tubules. Although in many of the cases there were not enough pigment casts to interfere seriously with renal function, nevertheless in our experience the presence of these casts has been the most diagnostic anatomic feature of renal insufficiency following transfusion. There was some degeneration of the epithelium adjacent to the casts, and necrotic cells were occasionally unassociated with casts. This was not striking in any of the cases studied. In two cases considerable hemosiderin was deposited in the tubular epithelium. Dilatation of convoluted tubules was usually present and marked. Many of the tubules were lined with low cuboidal epithelium, suggesting either a previous sloughing of the superficial portion or regeneration of cells. Mitotic figures, however, were found only with difficulty. Occasional tubules contained polymorphonuclear leukocytes. The glomerular tufts appeared essentially normal.

In two of the cases the kidneys were so badly damaged by the primary renal lesion that the lesions incident to the transfusion reaction were overshadowed except for the presence of scattered pigment casts.

Qualitatively, the characteristics were essentially the same as those observed in the dogs, except that in the human kidneys there were frequent hemorrhages into the tubular lumens which were not present in the dogs. Neither the accumulation of pigment debris in the tubular lumens nor the necrosis of epithelium was as marked as in the dog kidneys. A satisfactory anatomic basis for the renal insufficiency was often lacking in the human material.

COMMENT

In our experiments on hemoglobinuria in dogs the chemical evidence and the clinical course indicated fairly clearly that death was the result of renal insufficiency. No significant anatomic changes outside the kidneys were noted except in two dogs which showed some necrosis of

TABLE 3—Summary of Anatomic Data for Human Beings Quantitatively Compared with Those for Dogs¹

Cases	Diagnoses	Sex	Age, Years	Days Lived After Transfusion	Chemical Evidence of Uremia in Blood	Liver			Kidneys					Interpretation of Anatomic Changes in Terms of Renal Function
						Ne crosis	Hemo siderosis	Tubulodilatation	Pigment crystals	Pigment tubulocrosis	Tubulonecrosis	Mitoses in Epithelium	Interstitial edema	
Our case 1 W B	Duodenal ulcer	M	65	10	Urea nitrogen, 188.4 mg creatinine, 17.6 mg	+	0	+	+	0	p	p	+	Toxic injury, changes not extensive
					Urea nitrogen, 155.4 mg creatinine, 12.3 mg	0	+	±	±	0	p	0	p	Toxic injury, changes not extensive
					Urea nitrogen, 105.7 mg creatinine, 11.4 mg	0	0	+	p	0	?	0	0	Damage complicated by prior nephritis
					Urea nitrogen, 130.2 mg creatinine, 10.3 mg		0	+	±	0	?	0	0	Damage complicated by prior nephritis
					Urea nitrogen, 119 mg creatinine, 8.7 mg	+	0	p	+	0	0	0	p	Toxic injury, changes not extensive
Weinstein's case	Prostatic resection	M	60	6	Urea nitrogen, 140 mg creatinine, 10.4 mg		±	+	+	0	0	0	0	Pigment obstruction, factor in uremia
					Urea nitrogen, 344 mg creatinine, 16.2 mg	0	+	+	+	0	p	0	±	Pigment obstruction, factor in uremia
Hassett's case	Abortion	F	26	12	Urea nitrogen 207 mg	+	+	+	+	0	p	0	±	Toxic injury, changes not extensive
						0	+	±	+	0	p	0	p	Toxic injury, changes not extensive
Moody's case	Aleukemic leukemia	M	37	25		0	+	±	+	0	p	0	p	Toxic injury, changes not extensive

* An attempt has been made to indicate the occurrence of the anatomic lesions quantitatively by direct comparison with the data for dog kidneys in tables 1 and 2 using the same scale + indicates less than 1, p present but less than ±, ? interpretation impossible because of prior lesions

the central zones of the hepatic lobules. The kidneys of six dogs (dogs 1, 2, 5, 12, 20 and 24) gave satisfactory evidence of extensive obstruction with pigment of the tubules in the region of the loops of Henle; there was a minimal amount of tubular necrosis. These six kidneys then, presented an anatomic picture of relatively pure obstruction with pigment. Physiologic disturbances, in addition to obstruction, cannot of course, be excluded on an anatomic basis. From the anatomic criteria the hypothesis of Baker and Dodds⁵ can explain these lesions. These writers have demonstrated that hemoglobin forms a precipitate in solutions comparable to urine with an acid reaction. Richards and Walker¹¹ have stated that the glomerular filtrate in the amphibian tubule first becomes acid in the region of Henle's loop. This location for the dog's kidney can be only inferred at present, but the assumption of a similar situation will explain the lesion which we have described. The hypothesis will also explain why dogs which were given transfusions when the urine was alkaline did not show renal lesions.

In three other dogs (dogs 11, 21 and 23) there was evidence of a severe grade of tubular necrosis as well as some obstruction with pigment. Of these, only dog 11 had hepatic necrosis. In dog 23 the tubular necrosis overshadowed the obstruction so completely that we were forced to the conclusion that the latter process could not have produced serious interference with renal function.

From our anatomic studies of dogs we conclude that the mechanism of obstruction of renal tubules with hemoglobin pigment may be the chief cause of renal insufficiency but that there is another, probably independent, process operating which causes tubular necrosis and which may be severe enough to cause death.

The deposition of hemosiderin in the tubular epithelium has impressed some authors¹² as being a possible cause of impaired function. In our studies of dogs this seems to be a part of the physiologic process which occurs whenever hemoglobin is free in the blood stream. The pigment is taken up not only by the tubular epithelium of the kidney but also by the Kupffer cells in the liver and by the reticulo-endothelium of the spleen and lymph nodes. When repeated injections are given, hemosiderin is aggregated in masses of mononuclear cells in the parenchyma of the liver and the interstitial tissue of the kidney. It does not appear, however, that this process leads to impairment of function. Renal insufficiency occurred in some dogs with only minor grades of hemosiderosis.

11 Richards, A. N., and Walker, A. M. Urine Formation in the Amphibian Kidney, *Am J M Sc* **190** 727-746 (Dec) 1935.

12 Lichty, J. A., Havill, W. H., and Whipple, G. H. Renal Thresholds for Hemoglobin in Dogs, *J Exper Med* **55** 603-615 (April) 1932. Bordley.³

TABLE 4—Summary of Anatomic Data for Cases Described by Various Authors *

Authors	Case No.	Diagnosis	Sex, Age, Yr	Days Lived After Fusion	Chemical Evidence in Blood of Uremia	Liver		Kidneys					Authors' Interpretation
						Ne crosis	Hemo siderosis	Tubu lar Dilation	Pig ment Crystals	Tubu lar Necrosis	Regene rating Epithelium	Inter stitial Edema	
Bondley ³	3	Pernicious anemia	M 39	10	Nonprotein nitrogen, 186 mg., creatinine, 10.1 mg.	+	+	+	+	+	+	+	
Goldring and Griffiths ^{13b}	1	Diabetic gangrene	M 55	7	Nonprotein nitrogen, 162 mg.	+	+	+	+	+	+	+	Acute nephrosis
Goldring and Griffiths ^{13b}	4	Puerperal sepsis	F 24	19	Nonprotein nitrogen, 245 to 180 mg.	0	—	—	+	+	0	+	Acute nephrosis
Baker and Dodds	1	Gastric ulcer	F 38	1	Nonprotein nitrogen, 206 mg., creatinine, 6 mg.	0	—	+	+	0	0	0	Pigment obstruction
Baker and Dodds ²	2	Cholelithiasis with jaundice	F 54	17	Nonprotein nitrogen, 800 mg., urea, 920 mg., creatinine, 26 mg.	0	—	0	0	+	0	0	Pigment obstruction plus some other factor
Witts ^{13a}		Postpartum anemia	F 29	11	Urea, 354 mg.	—	+	+	+	+	+	+	"Hemoglobin infarction of the kidneys"
Shera ^{13a}		Ruptured ectopic pregnancy	F 36	8	Urea, 174 mg (3d day)	0	—	+	+	+	0	0	Pigment obstruction
Payne ^{13a}		Acute hemolytic anemia	M 20	3	Urea, 157 mg.	0	—	+	+	+	0	0	"Hemoglobin infarction of the kidneys"
Emke ^{13a}	1	Ruptured tubal pregnancy	F 32	6		+	—	0	+	0	0	—	Pigment obstruction
Luge and Herrlich	1	Posthemorrhagic anemia	M 9	9	Urea, 100 mg.								"Hemoglobin infarction of the kidneys"
Luge and Herrlich	2	Acute mastoiditis	F 6	2	Urea, 203.5 mg.								"Blockage of the tubules," "Blockage of the tubules"
Landa ^{13a}	1	Gastric hemorrhage	M 33	5	"Rest nitrogen," 234 mg.	+	+	0	+	+	—	—	
Landa ^{13a}	2	Cholelithiasis	F 28	9	"Rest nitrogen," 150 mg.	—	+	0	+	+	—	—	
Landa ^{13a}	3	Hypernephroma	M 64	1½		+	0	—	—	+	—	—	
Terplan and Givert ²		Quinine hemo globinuria and pregnancy	F 41	Not known	Urea nitrogen, 344 mg., creatinine, 16.2 mg.	0	+	+	+	+	0	—	"Distention of tubular system by masses of hemoglobin"

* + indicates described or implied as present, 0, described or implied as not present —, not mentioned

We have incorporated in table 4 the principal anatomic features described by several authors¹³ in isolated cases of human beings who died as a result of renal insufficiency following reactions due to blood transfusion or, in one case, following quinine hemoglobinuria. No attempt has been made to record the various lesions quantitatively, as this is manifestly impossible without studying the tissues at first hand with reference to a large series of cases. The tabulation illustrates three points: first, that most of the kidneys described resembled each other qualitatively as to the types of lesions present, second, that the quantitative relation of the various lesions must have varied considerably, as inferred from the author's final anatomic diagnosis, and, third, that the anatomic study of from one to three cases does not constitute a safe basis for generalization as to the etiology of the condition.

With separate anatomic pictures of obstruction with pigment and of a necrosing process available in our experimental material for comparison, the histologic studies of the kidneys of nine human beings who died of renal insufficiency after hemolysis has tended to clarify some of the questions relating to etiology. In all the patients there was evidence that the precipitation of hemoglobin pigment in the tubular lumens had occurred to a slight degree at least. But in most of the cases not enough tubules were obstructed to produce any important diminution in renal function. Two of the patients, however, had enough tubules obstructed to have been a possible factor in producing death. Nevertheless, the presence of pigment casts and of hemosiderosis is an important criterion in making the anatomic diagnosis of transfusion nephropathy. The predominant lesions were more often degenerative changes in the tubules and interstitial edema. In many of the cases the anatomic changes were slight and did not appear adequate to explain the renal insufficiency.

Another point to be kept in mind in comparing the human and dog kidneys was that the dose of hemoglobin administered to the dogs was probably at least twice as much as that administered to most of the patients on the basis of body weight. It should also be remembered

13 (a) Bordley³ (b) Goldring, W., and Graef, I. Nephrosis with Uremia Following Transfusion with Incompatible Blood. Report of Seven Cases with Three Deaths, *Arch Int Med* **58** 825-845 (Nov.) 1936. (c) Baker and Dodds⁵ (d) Witts, L. J. A Note on Blood Transfusion, with an Account of a Fatal Reaction, *Lancet* **1** 1297-1299 (June 22) 1929. (e) Shera, G. Fatal Suppression of Urine Caused by Latent Hemagglutinins, *Brit M J* **1** 754-755 (May 5) 1928. (f) Payne, R. V. Acute Hemolytic Anemia. Death After Transfusion, *Guy's Hosp Rep* **84** 65-71 (Jan.) 1934. (g) Lemke, R. Pathologisch-anatomische Befunde bei Todesfällen nach Bluttransfusionen, *Virchows Arch f path Anat* **257** 415-429, 1925. (h) Liege, R., and Herr, A. Les nephropathies graves post-transfusionelles, *Ann de med* **34** 398-420, 1933. (i) Lindau, A. Reaktionen nach Bluttransfusion. Eine etiologische und pathologisch-anatomische Studie, *Acta path et microbiol Scandinav* **5** 382-427, 1928. (j) Terplan and Javert²

that there are some chemical differences between human and canine hemoglobin which might account for some of the discrepancies noted. It should be pointed out that in the kidneys of dogs 12 and 20 we had illustrations of the amount of obstruction with pigment which was less than the minimum amount necessary to produce death, as these dogs were killed when they were recovering from renal insufficiency.

CONCLUSIONS

The transfusion of canine hemoglobin into dogs when the urine is acid results in death from renal insufficiency. This does not occur when the urine is alkaline at the time of the transfusion.

The anatomic picture of obstruction of the renal tubules by hemoglobin pigment sufficient to be the chief cause of the renal insufficiency is observed in most dogs under the experimental conditions outlined. A nephrotoxic process often operates and may cause renal insufficiency independently.

The deposition of hemoglobin pigment as hemosiderin in the renal tubules and in the reticulo-endothelial system apparently does not contribute to the development of renal insufficiency.

An anatomic study of the kidneys of nine human beings who died of renal insufficiency after hemolysis revealed the two independent mechanisms seen in dogs, the obstruction with pigment and the necrotizing factor.

In occasional human beings the precipitation of hemoglobin pigment in the tubules is extensive and may be a cause of renal insufficiency. This complication could probably be prevented by alkalinizing the urine prior to the transfusion.

The renal insufficiency after hemolysis in the majority of human beings is probably caused by some nephrotoxic substance which causes degeneration of tubular epithelium and interstitial edema.

Dr. E. T. Bell, Professor of Pathology at the University of Minnesota, examined the tissue sections and offered valuable suggestions. Drs. M. F. Hassett of St. Paul, M. L. Weinstein of Chicago, K. L. Terplan of Buffalo and A. M. Moody of San Francisco furnished material from their patients.

ASSOCIATION OF HYPERTHYROIDISM WITH PULMONARY TUBERCULOSIS

A REVIEW OF THE LITERATURE AND REPORT OF
TWENTY-THREE CASES

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The relation of the thyroid gland to tuberculosis has received much attention in the literature since about the middle of the last century. Clinical, experimental and pathologic observations have produced a diversity of opinions concerning this relation. It is our purpose to review briefly the more important views expressed in the literature and to present clinical observations on the progress of 23 patients with coexistent hyperthyroidism and pulmonary tuberculosis.

REVIEW OF THE LITERATURE

Earlier writers (Virchow, Rokitsansky and Hamburger¹) believed an antagonism exists between tuberculosis and the thyroid gland and that the latter is immune to invasion. Infections of various types may produce diffuse temporary swelling of the thyroid and congestion or colloid goiter. This seems to be particularly true in cases of tuberculosis, in which parenchymatous or colloid goiter is relatively common². Such a goiter may recede as the tuberculosis heals, but if the tuberculosis progresses there may develop in the later stages a diffuse sclerosis of the thyroid gland and in some instances, late in tuberculosis, evidence of thyroid insufficiency. In some instances diffuse sclerosis of the endocrine system has been associated with tuberculosis, in such cases it is possible that changes in the thyroid gland may have been due in part to lesions in other endocrine organs (i e, the anterior lobe of the pituitary gland³). The clinical picture of mild hyperthyroidism is fre-

From the Sections on endocrine and thoracic disorders of the Medical Clinic, the Hospital of the University of Pennsylvania.

1 Virchow, Rokitsansky and Hamburger, cited by Epstein^{4b}

2 Brown, P. K. Hyperthyroidism and Tuberculosis, *Tr. Am. Climat. & Clin. A.* **37** 37, 1921.

3 Jedlička, V. Relation of the Thyroid Gland to Tuberculosis, *Časop. lek. česk.* **75** 1521, 1936.

quently seen in cases of early tuberculosis and may confuse the diagnosis. The earlier belief that the association of tuberculosis and frank hyperthyroidism is a rarity⁴ has been disproved by numerous later reports, but it seems to be true that active pulmonary tuberculosis and frank thyrotoxicosis are not commonly encountered in the same patient. Jedlička³ has recently written an extensive review of the entire subject of the relation of the thyroid gland to tuberculosis.

Experimental Studies—The protective action of the thyroid gland against tuberculosis has been studied experimentally, with conflicting results. Steinback,⁵ Suzuki and Hanaoka,⁶ Ishimaru⁷ and others⁸ have produced evidence suggesting that the presence of the thyroid gland or the administration of thyroid substance assists body defense against tuberculosis in the experimental animal. Schedtler,⁹ however, found attenuation of tuberculosis in guinea pigs and rabbits after thyroid ablation, and Galli¹⁰ found that thyroidectomized guinea pigs survived bovine tuberculosis longer than did controls. Gloyne's¹¹ work led him to express the belief that there is little reason to attribute a direct antitoxic action to the thyroid gland in tuberculosis.

Evidence has been found of hypertrophy¹² and hyperfunction¹³ of the thyroid gland in experimental tuberculosis. Ishimaru⁷ found in

4 (a) West, Samuel. Thirty-Eight Cases of Exophthalmic Goitre, with Remarks, *Tr Ophth Soc U Kingdom* **6** 76, 1886. (b) Epstein, D. Tuberculose und endokrines System, *Ztschr f Tuberk* **72** 383, 1935.

5 Steinback, M. M. Experimental Tuberculosis in the Albino Rat. The Comparative Effects of Avitaminosis, Suprarenalectomy and Thyroid-Parathyroidectomy in Experimental Tuberculosis, *Am Rev Tuberc* **26** 52, 1932.

6 Suzuki, K., and Hanaoka, M. Studies on the Relation Between the Function of Internal Secretion and Tuberculous Infection. The Tuberculous Infection in the Case of Abnormality of Function of Hypophysis and Thyroid Gland, *Tr Soc path jap* **24** 415, 1934.

7 Ishimaru, Y. Effect of Tuberculous Infection on the Tissues of the Thyroid and Thymus Glands, *Kekkaku* **13** 7 (March 25) 1935.

8 Marbé, S. Les opsonines dans les états thyroïdiens. I. Les opsonines des animaux hyperthyroïdes, *Compt rend Soc de biol* **64** 1058, 1908. Stepanoff. Le corps thyroïde et les défenses naturelles de l'organisme, *ibid* **66** 296, 1909. Bernard, Suzanne. Glande thyroïde et tuberculose. Influence de la thyroïdectomie sur l'évolution de la tuberculose expérimentelle chez le lapin, *Thesis, Paris*, no 55, 1921.

9 Schedtler, D. Tuberkuloseablauf und Schilddrüsenfunktion, *Ztschr f Tuberk* **70** 314, 1934.

10 Galli, R. Tiroidectomia e decorso delle infezioni. Studio morfologico delle reazioni cellulari negli animali stiroidati, *Arch ital di chir* **41** 571, 1935.

11 Gloyne, S. R. Experimental Tuberculosis, *J Path & Bact* **28** 451, 1925.

12 Webb, G. B. Immunity in Tuberculosis, *J Lab & Clin Med* **1** 414, 1916.

13 Hashimoto, T. Study of Function of Thyroid Glands of Tuberculous Rabbits, *J Orient Med* **25** 81, 1936.

guinea pigs that as the infection progressed the picture of partial hyperfunction (colloid goiter) appeared and was followed in the late stages by atrophic and degenerative changes. He also found that thyroidectomized animals infected with tuberculosis showed more marked regressive changes in the thymus and adrenal glands than did non-thyroidectomized controls. Conversely, thymectomized animals showed degenerative changes in the thyroid gland.

Frommel, Herschberg and Trottet¹⁴ found that tuberculin hastened the metamorphosis of tadpoles somewhat but did not affect the growth or epiphyseal development of young rabbits and guinea pigs. They also found that a single injection of tuberculin often caused tachycardia and thyroid congestion in guinea pigs, no response occurred after thyroid ablation.

Iodine Content of the Thyroid Gland in Tuberculosis—Labbé, Vitry and Giraud¹⁵ found a wide variation in the iodine content of the thyroid glands of 24 persons who had died of tuberculosis. This did not seem to be influenced by iodine therapy. In general, the iodine content was greater in cases of rapidly progressive than in cases of more chronic tuberculosis, leading the authors to postulate a condition of thyroid exhaustion in the latter. Piazza¹⁶ found the iodine content of the thyroid glands of persons who had died of tuberculosis to be greater in relation to the total weight of the gland than that of the thyroid glands of persons dying of other causes.

Basal Metabolism in Pulmonary Tuberculosis—This has been extensively studied, again with conflicting conclusions. Raimondi and Scartascini¹⁷ concluded that the basal metabolic rate tends to rise with the progress of tuberculosis and to fall as healing occurs. They found a sharp drop in the metabolic rate after pneumothorax. (In this connection the findings of Abbott and his associates¹⁸ are interesting. They reported a "reversion" of the thyroid gland to the colloid state in 31 per cent of puppies and 57 per cent of kittens after pneumothorax and oleothorax but no changes in the thyroid gland in adult dogs and cats.

14 Frommel, E., Herschberg, A. D., and Trottet, A. Tuberculine et thyroïde. Étude expérimentale—deductions thérapeutique, *Rev de la tuberc* **11** 399, 1935.

15 Labbé, H., Vitry, G., and Giraud, G. Dosage de l'iode contenu dans les corps thyroïdes des tuberculeux. *Compt rend Soc de biol* **65** 371, 1908.

16 Piazza, R. Il contenuto in iode della tiroide nei tubercolotici. *Riforma med* **49** 325, 1933.

17 Raimondi, A. A., and Scartascini, R. El metabolismo basal en la evolución de la tuberculosis pulmonar, *Prensa méd argent* **22** 21 (Jan 2) 1935.

18 Abbott, A. C., Goodwin, A. M., Meltzer, S., and Stephenson, E. Effect of Pneumothorax and Oleothorax on the Histologic Structure of the Thyroid Gland, *Arch Surg* **30** 667 (April) 1935.

after such procedures) Cordier ¹⁹ stated the opinion that sudden elevation of the basal metabolic rate (fever being excluded as a cause) is a bad prognostic sign in tuberculosis Charosky, ²⁰ in a study of 240 patients, found the greatest increase in the metabolic rate in patients with active fibrocaceous lesions McBrayer ²¹ and Moraldi ²² found an increased rate in a large percentage of their patients

On the other hand, Izzo, Lanz and Casanegra ²³ found the basal metabolic rate within normal limits in 83 per cent of 116 cases and concluded that when an elevation occurs it is in proportion to the elevation of the temperature They said they felt that pulmonary tuberculosis itself does not exert any effect on basal metabolism McCann and Barr ²⁴ stated that the basal metabolic rate may be normal or slightly increased in tuberculosis and that in this disease the loss of weight may cause a drop in the metabolic rate which more than compensates for the tendency to an increase in the rate caused by the infection Olivier and Skladal ²⁵ found no correlation between the elevation of the basal metabolic rate and the severity of the tuberculosis and concluded that a normal rate does not necessarily indicate a stabilization of the tuberculous process McMahon ²⁶ found an increased basal metabolic rate only in cases of advanced tuberculosis Marsh ²⁷ reported normal rates in cases of advanced tuberculosis Makinen ²⁸ compared findings for 142 patients with pulmonary tuberculosis (928 determinations) with those for 10 normal subjects (75 determinations) He

19 Cordier, V Metabolisme basal des tuberculeux, Compt rend Soc de biol **88** 782, 1923

20 Charosky, Leon Metabolismo basal en la tuberculosis pulmonar Consideraciones sobre 240 casos, Rev Asoc méd argent **48** 1256, 1934

21 McBrayer, R A Blood Sugar and Basal Metabolism Findings in Chronic Pulmonary Tuberculosis and Hyperthyroidism, J A M A **77** 861 (Sept 10) 1921

22 Moraldi, M Osservazioni sul metabolismo basale nella tubercolosi pulmonare, Tuberculosis **24** 329, 1932

23 Izzo, R A , Lanz, P, and Casanegra, A El metabolismo basal en la tuberculosis pulmonar, Semana med **2** 1092 (Oct 11) 1934

24 McCann, W S, and Barr, D P Clinical Calorimetry XXIX The Metabolism in Tuberculosis, Arch Int Med **26** 663 (Dec) 1920

25 Olivier, H R, and Skladal, J Étude du métabolisme basal dans 30 cas de tuberculose pulmonaire, Ann de méd **34** 307, 1933

26 McMahon, A Basal Metabolism in Pulmonary Tuberculosis, Tr Am Therap Soc **31** 221, 1931

27 Marsh, M E Respiratory Metabolism and Pulmonary Ventilation in Pulmonary Tuberculosis, J Lab & Clin Med **18** 599, 1933

28 Makinen, N Beitrage zur Kenntnis uber der Grundumsatz bei Lungentuberkulose, Acta Soc med fenn duodecim (Ser B, pt 1, Art 1) **18** 1, 1933

found no correlation between the metabolic rate and the stage or pathologic type of tuberculosis or the sedimentation rate

Cholesterol Content of the Blood in Tuberculosis—The cholesterol content of the blood is almost constantly increased in hypothyroidism and is often decreased in hyperthyroidism²⁹ Variations in the cholesterol content in tuberculosis are of interest and of possible importance in connection with these facts, although further study is necessary to determine any significant relation It is generally agreed³⁰ that in active tuberculosis the cholesterol level is lowered, the lowest figure being obtained in the ulcerative forms with exudation^{30c} Healing is accompanied with a rising level Lumbreras and Morante^{30c} stated that a rise occurs also in tuberculous meningitis They found no relation between the cholesterol content of the blood and the sedimentation rate or the bacillary content of the sputum and no definite relation between blood sugar and blood cholesterol in tuberculosis Leonardi^{30a} stated as his opinion that the body defenses are augmented by hypercholesteremia and that an increase in the ratio between cholesterol ester and free cholesterol is a favorable prognostic sign Osato, Kurashige and Sakurai³¹ found an increase in the fatty acid and cholesterol contents of the lungs and liver of tuberculous subjects, with a marked increase in the adrenal glands Steinberg^{30d} reported a fall in blood cholesterol values within forty-five days ante mortem in 17 of 20 persons dying of tuberculosis

Thyroid Opothecapy in Tuberculosis—Greenfield,³² in 1893, and Morin,³³ in 1895, suggested the administration of thyroid substance in the treatment of tuberculous patients A similar suggestion was made

29 Hurxthal, L M Blood Cholesterol and Thyroid Disease Myxoedema and Hypercholesteremia, *Arch Int Med* **53** 762 (May) 1934

30 (a) Leonardi, S La colessterina nel sangue e nell'espettorato dei tubercolotici polmonari, *Morgagni* **77** 683 (June 23) 1935 (b) Ceccarelli, Danilo Ricerche sulla colessterinemia nei soggetti affetti da tubercolosi polmonare, *Tuberculosis* **25** 414, 1933 (c) Lumbreras, R B, and Morante, A F Colessterinemia y glicemia en los enfermos tuberculosis, *Arch de med, cir y especialid* **37** 1365 (Dec 15) 1934 (d) Steinberg, I R La colessterinemia en los períodos pre-agómicos de la tuberculosis, *Semana méd* **2** 1225 (Oct 24) 1935 (e) Eyza-guirre y E, G La colessterina en la tuberculosis pulmonar, *Crón méd, Lima* **53** 3, 1936

31 Osato, S, Kurashige, T, and Sakurai, H Fettstoffwechsel des tuberkulösen Organismus I Mitteilung, Untersuchungen über die Fett- und Lipoidverteilung in den Organen und Geweben des tuberkulösen Organismus, *Jap J M Sc (VIII, Int Med, Pediat & Psychiat)* **4** 123, 1936

32 Greenfield, W S Some Diseases of the Thyroid Gland, *Lancet* **2** 1553, 1893

33 Morin Physiologie et medication thyroïdiennes, *Rev med de la Suisse Rom* **15** 241 (May 20) 1895

by Webb and his associates³⁴ in 1921 Coulaud³⁵ reported on 3 patients with nontuberculous arthritis in whom active pulmonary tuberculosis developed after they received thyroid therapy, he quoted references to 3 similar cases reported in the literature Dalto and Charosky³⁶ gave 0.2 Gm of a thyroid preparation daily for five days to 31 patients with pulmonary tuberculosis, only 3 showed a rise in pulse rate Several writers have commented on the susceptibility of persons with hypothyroidism to tuberculosis Schedtler,³ however, found no such relation and stated that there is no basis for the treatment of tuberculous patients with thyroxin

Pathologic Picture of the Thyroid Gland in Tuberculosis—The subject of tuberculosis of the thyroid gland has been so extensively reviewed³⁷ that it requires only brief mention here This condition is relatively rare (0.1 per cent of 20,758 glands examined at the Mayo Clinic^{37a}), it affects women chiefly and it has a varied symptomatology, seldom being diagnosed clinically It may be associated with toxic or nontoxic goiter, but whether coincidentally or as an etiologic agent is uncertain It is believed to be hematogenous and usually secondary to a tuberculous focus elsewhere Diffuse or isolated tubercles, caseation, abscess or diffuse sclerosis may be present Of 125 cases, reports of which were collected by Rankin and Graham,^{37a} active tuberculosis was known to be present in 6 and to be suspected in 5 others

Coulaud³⁸ studied the thyroid glands of 120 tuberculous patients, with the findings presented in table 1 He stated that he had never seen the histologic picture of hyperthyroidism in the thyroid gland of a tuberculous subject Roger and Garnier³⁹ reported marked sclerosis with periaarteritis and endarteritis in the thyroid glands of 4 tuberculous subjects

34 Webb, G. B., Gilbert, G. B., and Ryder, C. T. The Adrenals and Thyroid in Experimental Tuberculosis, *Am Rev Tuberc* **5** 266, 1921

35 Coulaud, E. L'opotherapie thyroïdienne et tuberculose, *Ann de med* **10** 385, 1921

36 Dalto, A., and Charosky, L. La prueba de la tiroidina en la tuberculosis pulmonar, *Prensa méd argent* **20** 1593 (July 19) 1933

37 (a) Rankin, F. W., and Graham, A. S. Tuberculosis of the Thyroid Gland, *Ann Surg* **96** 625, 1932 (b) Collier, F. A., and Huggins, C. B. Tuberculosis of the Thyroid Gland, *ibid* **84** 804, 1926 (c) Starlinger, F. Cases of Tuberculosis of the Thyroid Gland, *Wien med Wchnschr* **83** 439, 1933 (d) Sehmisch, W. Schilddrüsentuberkulose und Basedow, *Deutsche Ztschr f Chr* **243** 693, 1934 (e) Jedlička³

38 Coulaud, E. Le corps thyroïde des tuberculeux, *Bull et mem Soc med d hop de Paris* **44** 1551 (Dec 17) 1920

39 Roger, H., and Garnier, M. La sclerose des corps thyroïdes chez les tuberculeux, *Compt rend Soc de biol* **5** 873, 1898

From Jan 1, 1930, to Sept 1, 1936, 7,763 necropsies were performed in the University of Pennsylvania service at the Philadelphia General and University of Pennsylvania hospitals, 1,268 of these were on persons who died of tuberculosis or its complications. In 108 of the reports the thyroid gland was described either grossly or microscopically. The data are presented in table 2. It will be seen that no instance of hyperthyroidism and coexistent active pulmonary tuberculosis was found. During the same period necropsy was performed on 18 persons who died

TABLE 1—*Pathologic Changes in the Thyroid Gland in Tuberculosis (Coulaud)*

Pathologic Changes	Number of Patients
Tuberculosis	3
Cystic goiter	3
No definite change	12 (most rapidly fatal tuberculosis)
Increased connective tissue (slight)	14
Large areas of sclerosis (patchy)	6
Diffuse sclerosis	35 (mostly chronic tuberculosis)
Regeneration	45 (slow involution of tuberculosis in most)
Phlegmon	2

TABLE 2—*Condition of Thyroid Glands of One Hundred and Eight Patients Who Died of Pulmonary Tuberculosis or Its Complications*

Condition of Thyroid Gland	Type of Tuberculosis					
	Active (Adults)		Healed (Adults)		Active (Children)	Miscellaneous (Pleurisy, etc.)
	Gross	Microscopic	Gross	Microscopic	Microscopic	Microscopic
Normal	59	9	4	4	2	
Colloid goiter		1				
Fibrosis		2		1		1
Hypoplasia		1				
Calcification	1					
Atrophy and fibrosis	4	6				
Acute congestion		1				
Adenomatosis	2	2				
"Degeneration"		1				
Chronic thyroiditis		1				
Hypertrophy	1		1			
Adenoma with fibrosis		1				
Atrophy	1		1			
Toxic hyperplasia				1		

of hyperthyroidism or its complications. Among these, 2 showed healed apical tuberculosis, 1 a healed Ghon tubercle of the lower lobe and 1 tuberculous mediastinal adenitis. No instance of active pulmonary tuberculosis was found.

Hyperthyroidism and Pulmonary Tuberculosis—Most writers agree that the association of frank hyperthyroidism with active pulmonary tuberculosis is uncommon. The incidences reported vary from 0.25⁴⁰

⁴⁰ von Massur, F. W. Relation of Thyroid Changes to Origin and Course of Chronic Pulmonary Tuberculosis, *Beitr. z. Klin. d. Tuberk.* 39:45, 1918-1919.

to 15 per cent ^{4b} Rink ⁴¹ reported an incidence of less than 1 per cent in 12,976 cases of pulmonary tuberculosis. The appearance of a mild transient picture of hyperthyroidism (forme fruste) with goiter and elevation of the basal metabolic rate is not uncommon, however, early in tuberculosis, especially in young women. This has been regarded as evidence of an active defense mechanism and has been correspondingly thought to be of good prognostic significance ⁴². The signs and symptoms usually subside as the tuberculous lesion either progresses or heals. Steck ⁴³ studied the reinforcing effect on epinephrine vasoconstriction of blood from normal persons, thyrotoxic patients and tuberculous patients with and without "Basedow-like" symptoms. He concluded that the thyroid gland does not play a part in producing the "thyrotoxic" symptoms often seen in tuberculosis. The difficulty of making a differential diagnosis between hyperthyroidism and early tuberculosis has received much attention ⁴⁴. Many of the signs and symptoms of early tuberculosis (tachycardia, loss of weight, nervousness and vasomotor phenomena) have been ascribed to a direct stimulating effect of the infection on the thyroid gland ⁴⁵. Pulmonary tuberculosis is regarded as an important and often overlooked cause of hyperthyroidism by some writers ⁴⁶. Others ⁴⁷ believe that no significant relation exists between the two diseases.

Opinion is divided as to the effect of hyperthyroidism on the prognosis of coexistent tuberculosis. Fishberg, ⁴⁸ Rink, ⁴¹ Lissner, ^{44b} Rich-

41 Rink, W. Lungentuberkulose und Schilddrüsenerkrankungen, *Tuberkulose* **13** 179, 1933.

42 (a) Richard, G. Syndromes basedowiens et tuberculose, *Rev franç d'endocrinol* **12** 199, 1934. (b) Leitner, J. Tuberkulose und innere Sekretion, *Zentralbl f d ges Tuberk-Forsch* **41** 1, 1935.

43 Steck, H. Recherches expérimentales sur les relations hypothétiques entre la maladie de Basedow et la tuberculose, *Schweiz med Wchnschr* **51** 535 (June 9) 1921.

44 (a) Stévenin, H., and Franchel, F. Hyperthyroïdie et tuberculose pulmonaire, *Monde méd, Paris* **46** 649 (April 15) 1936. (b) Lissner, H. The Relation of the Ductless Glands to the Incidence and Development of Tuberculosis, *Am Rev Tuberc* **29** 249, 1934. (c) Frank, L. W. Tuberculosis and Toxic Goiter, *ibid* **25** 49, 1932. (d) Roberts, S. R. The Determination of Tuberculosis and Toxic Goiter, *ibid* **23** 120, 1931.

45 Marañón, G. Hipertiroidismo y tuberculosis, *Crón méd mex* **31** 829 (Sept.) 1932. Epstein ^{4b}.

46 Saathof, L. Thyreosis und Tuberkulose, *München med Wchnschr* **60** 230, 1913.

47 Gruner, S. Die Beziehungen zwischen Lungentuberkulose und den Erkrankungen der Thyreoidae, *Ztschr f Tuberk* **53** 319, 1929.

48 Fishberg, M. *Pulmonary Tuberculosis*, ed 4, Philadelphia, Lea & Febiger, 1932, vol 2, pp 217-219.

and ^{42a} and others have stated the opinion that the course of tuberculosis is favorable when hyperthyroidism is present. Lissner ^{44b} and Fishbein ⁴⁸ have emphasized the susceptibility of myxedematous persons to tuberculosis. A corollary to these views is the belief that tuberculous patients with toxic goiter should be treated conservatively and that thyroidectomy in such cases is likely to be followed by rapid progress of the pulmonary process ⁴⁹. On the contrary, hyperthyroidism is regarded by several authors ⁵⁰ as an aggravating factor. Thyroidectomy has been advocated by Crile, ⁵¹ Cattell and Meredith, ⁵² Roberts, ^{44d} Sloan ⁵³ and others. Crile reported that of 87 patients with tuberculosis and hyperthyroidism, 74.5 per cent of those in whom the diagnosis of tuberculosis was confirmed roentgenographically showed definite improvement after thyroidectomy. Of those followed postoperatively by means of roentgenograms, 82 per cent showed improvement and 35 per cent cure.

REPORT OF CASES

During the period from Jan. 1, 1930, to Sept. 1, 1936, 1,053 patients with hyperthyroidism were admitted to the Hospital of the University of Pennsylvania. Among them were 14 with pulmonary tuberculosis (diagnosis based on roentgen findings and positive results of examination of the sputum or physical signs), an incidence of 1.3 per cent. During approximately the same period (Jan. 1, 1930, to Dec. 1, 1936), among 729 patients with pulmonary tuberculosis, active and arrested the incidence of hyperthyroidism (14 cases) was 1.9 per cent ⁵⁴.

We have reviewed the records of 23 thyrotoxic patients with associated pulmonary tuberculosis who were admitted to the hospital between

49 Hoffmann, H. Goiter and Tuberculosis, *Munchen med Wchnschr* **70** 1363, 1923.

50 Coulaud, E. Corps thyroïde et tuberculose, Thesis, Paris, Vigot frères, 1922. Sergeant, E., and Mignot, R. Hyperthyroïdie et tuberculose pulmonaire, *Rev de la tuberc* **6** 561, 1925. Ison, H. L. Hyperthyroidism in Tuberculosis, *M. Bull. Vet. Admin* **7** 1171, 1931.

51 Crile, G. W. Hyperthyroidism and Associated Diseases, *Surg., Gynec. & Obst.* **58** 272, 1934.

52 Cattell, R. B., and Meredith, J. M. The Management of Concomitant Hyperthyroidism and Pulmonary Tuberculosis, *S. Clin. North America* **16** 1537, 1936.

53 Sloan, E. P. Tuberculosis and Goiter, *J. A. M. A.* **88** 1954 (June 18) 1927.

54 The mortality from tuberculosis for the United States registration area is about 59 per 100,000. Although there are no accurate statistics on the number of cases of active tuberculosis—the morbidity rate—it is generally agreed that this figure is at least ten times the mortality rate. A conservative estimate therefore would be that the morbidity rate is at least 590, or practically 0.6 per cent, for the country as a whole. The figure is fairly uniform for the various sections of the country where tuberculosis is a reportable disease.

June 1924 and October 1935 Whenever possible these patients have been brought back for follow-up examination, which has included the making of roentgenograms of the chest, blood counts, estimations of the sedimentation rate, determinations of the basal metabolic rate, examinations of the sputum when feasible and physical examinations, with the aid of these findings and the interval history the progress of the two diseases has been determined

For purposes of analysis the patients have been divided into two groups Group 1 contains 10 patients in whom tuberculosis was considered active when they were first seen Group 2 contains 13 patients in whom tuberculosis was considered inactive when they were first seen Six patients died of tuberculosis from a month to eight and one-third years after admission to the hospital One patient died of a fractured skull There were no deaths attributable to hyperthyroidism The patients were referred back to their physicians or to sanatoriums for treatment of the tuberculosis There was no evidence of extrapulmonary tuberculosis in any patient at the time of admission to the hospital No evidence of tuberculosis was seen in any of the thyroid glands removed at operation, serial sections, however, were not made All patients operated on received iodine (compound solution of iodine or potassium iodide) as part of their preparation A local anesthetic was employed, supplemented by nitrous oxide or avertin

The pertinent data relating to our patients are presented in tables 3 and 4 and are summarized in table 5 It will be seen that all the patients in group 1 were women, most of them (7 of 10) under 40 years of age In these patients the response of the hyperthyroidism to treatment was not as good as is to be expected in cases of ordinary uncomplicated hyperthyroidism, only 3 patients being completely relieved and 1 remaining unimproved Treatment of the hyperthyroidism likewise did not, in general, favorably affect the pulmonary disease, only 2 patients showed slight improvement, and 3 died of tuberculosis, the remainder becoming worse or remaining unchanged One patient showed an acute postoperative exacerbation of the tuberculosis The patients in group 2 were older, only 4 being under 40 The effects of treatment on the hyperthyroidism were definitely better than in the patients in group 1 The course of the tuberculous processes was likewise more favorable Although 3 patients died of the pulmonary disease after activation (which occurred from three to seventy-nine months after thyroidectomy), 4 showed healing and 2 improvement The preoperative response to iodine was somewhat better than that of the patients in group 1

For many years it has been believed that the administration of iodides is contraindicated in tuberculosis because of the danger of pro-

TABLE 3—Clinical Data for Ten Patients with Pulmonary Lesions Considered Active When Patients Were First Seen

Patient	Age	Sex	Type of Goiter	Basal Metabolic Rate, %	Location of Lesion (Roentgenogram)	Physical Signs	Results of Examination of Sputum	Treatment of Thyroid Condition	Results	
									Hyperthyroidism	Tuberculosis
F D *	31	F	Nodular	-5	Both upper lobes	Present	Positive, lite	Subtotal thyroid ectomy	Improved for 4 mo	Died 52 mo after operation
F M *	32	F	Diffuse	+71	Entire left lung (pneumonia)	Present	Positive	Irradiation, iodine	Unimproved	Died 1 mo after admission
L S	33	F	Diffuse	+62	Upper lobe of right lung	Present	Positive	Two stage thyroid ectomy	Improved	Died 18 mo after first operation
E S *	24	F	Nodular	+39	Both upper lobes	Present	None	Lobectomy	Improved	Slight progression 87 mo after operation
V S	38	F	Diffuse	+52	Upper lobe of right lung	Present	Negative	Subtotal thyroid ectomy	Improved for 2½ mo	Unknown, patient not seen after 2½ mo
E H	44	F	Diffuse	+53	Both upper lobes	Present	Negative	Subtotal thyroid ectomy	Cured	Slight improvement 5 mo after operation
O D	42	F	Diffuse	+62	Upper lobe of right lung	Present	Negative	Two stage thyroid ectomy, irradiation, iodine	Partial improve ment, recurrence after operation	Slight progression 74 mo after first operation
I L	24	F	Diffuse	+45	Both upper lobes	Present	None	Two stage thyroid ectomy, irradiation, iodine	Improved	No marked change, tuberculo sis first found during postoper ative recurrence of hyper thyroidism
B G	63	F	Diffuse	+40	Both upper lobes	Question able	Negative	Subtotal thyroid ectomy	Cured	No change 13 mo after opera tion
F N	32	F	Diffuse	+31	Upper lobe of right lung	None	None	Iodine, irradiation	Cured	Improved 57 mo after treat ment was begun

* See discussion in the text

TABLE 4—Clinical Data for Thirteen Patients with Pulmonary Lesions Considered Inactive or Doubtfully Active When Patients Were First Seen

Patient	Age	Sex	Type of Goiter	Basal Metabolic Rate, %	Location of Lesion (Roentgenogram)	Physical Signs	Results of Examination of Sputum	Treatment of Thyroid Condition	Results	
									Hyperthyroidism	Tuberculosis
I M	60	M	Diffuse	+41	Both upper lobes	Questionable	Negative	Two stage thyroidectomy	Cured	Lesion disappeared 64 mo after operation
J D	65	F	Diffuse	+57	Upper lobe of left lung	None	None	Subtotal thyroidectomy	Marked improvement 1 mo after operation	Unknown, patient not seen after 4 mo
I L	45	F	Diffuse	+50	Both upper lobes	None	None	Subtotal thyroidectomy	Cured (mild postoperative hypothyroidism)	Lesion had disappeared 7 yr after operation
J A	41	M	Diffuse	+35	Upper lobe of left lung	None	None	Irradiation	Cured (mild symptoms)	Lesion almost disappeared 3 yr after treatment
M T	31	F	Nodular	+49	Both upper lobes	Present (upper lobe of right lung)	None	Bipolar ligation	Cured	Died of tuberculosis 100 mo after operation, acute exacerbation 72 mo after operation
A M	34	F	Diffuse	+32	Upper lobe of right lung	Questionable	None	Lobectomy	Marked improvement 8 mo after operation	Acute exacerbation 39 mo after operation, died 52 mo after operation
B F	57	F	Nodular	-1	Lower lobe of left, upper lobe of right lung	None	None	Lobectomy	Chemically relieved but metabolic rate up to +24% 34 mo after operation	Slight progression 34 mo after operation
C H	32	M	Nodular	+52	Both upper lobes	Present (upper lobe of right lung)	None	Lobectomy	Cured	Marked improvement 78 mo after operation
K W	44	F	Diffuse	+44	Both upper lobes	Questionable in upper lobe of right lung	None	Irradiation	Cured	Healed 72 mo after treatment
D L	48	M	Diffuse	+70	Both upper lobes	Present	Negative	Two stage thyroidectomy	Marked improvement	Improved 96 mo after operation
A K	48	F	Nodular	+31	Upper lobe of right lung	None	None	Subtotal thyroidectomy	Cured 7 mo after operation	No change, died of skull fracture 9 mo after operation
C H	37	F	Diffuse	+26	Upper lobe of right lung	None	None	Subtotal thyroidectomy	Cured 7 mo after operation	Progression 7 mo after operation
G L	30	F	Nodular	+45	Upper lobe of left lung	Questionable	Negative until exacerbation	Subtotal thyroidectomy	Improved	Activation with rapid spread through left lung and death 9 mo after operation

ducing an acute flare-up or extension. We have reviewed the records of all our patients (20) who received iodine for evidence of such an untoward effect without finding any clear evidence that the tuberculosis was influenced unfavorably. One patient showed an exacerbation soon after thyroidectomy, and 1 patient, desperately ill with tuberculous pneumonia and presenting a clinical picture of fulminating hyperthyroidism (to be discussed), failed to respond to iodine. In neither case, however, could iodine be blamed with certainty, as several other factors were involved.

TABLE 5—*Summary of Data in Tables 3 and 4*

	Number of Patients	
	Active Tuberculosis	Inactive Tuberculosis
Sex		
Males	0	4
Females	10	9
Follow up period	1 to 87 mo	4 to 100 mo
Treatment of hyperthyroidism		
Irradiation	2	2
One stage thyroidectomy	4	5
Two stage thyroidectomy	3	2
Lobectomy or adenectomy	1	3
Bipolar ligation		1
Effect of iodine on hyperthyroidism		
Favorable	7	10
Questionable	2	1
None	1	
Immediate postoperative course		
Normal	5	8
Unexplained fever	2	2
Exacerbation of tuberculosis	1	
Acute nontuberculous infection of respiratory tract		1
Course of tuberculosis after treatment of hyperthyroidism		
No change	3	1
Healed		4
Improved	2	2
Worse	1	2
Died	3	3
Unknown	1	1
Effect of treatment on hyperthyroidism		
Cured	3	10
Improved	6	3
Unimproved	1	

Except for somewhat prolonged febrile periods in 4 cases, 1 case of acute nontuberculous infection of the respiratory tract and 1 case of acute exacerbation of tuberculosis, the 19 patients operated on had an immediate postoperative course which was uneventful.

We wish to call attention to 3 patients, all with active pulmonary lesions who showed the clinical phenomena of hyperthyroidism but whose thyroid glands did not show the histologic picture either of thyrotoxicosis or of iodine response. Two showed "colloid adenomas" (possibly areas of cyclic hyperinvolution containing excess colloid). One of these patients had a normal basal metabolic rate but in all other respects appeared clinically thyrotoxic, she showed improvement, with

a gain of 11 pounds (5 Kg) four months after operation, but subsequently died of tuberculosis. The other patient had a basal metabolic rate of +39 per cent, her thyrotoxic symptoms were improved seven and one-fourth years after operation, but the tuberculosis had progressed somewhat.

The third patient was a woman of 30 who had lost weight and had shown signs of nervousness for two or three years. A cough had been present for a month. She showed exophthalmos, goiter, auricular fibrillation, tremor and vasomotor changes, and the basal metabolic rate was +74 per cent. Soon after she was hospitalized there developed consolidation of the lower lobe of the left lung and coincidentally glycosuria and hyperglycemia. The sputum contained large numbers of tubercle bacilli. The pulmonary process spread rapidly throughout the entire left lung. The thyrotoxic symptoms did not respond to iodine or small doses of roentgen rays, and she died one month after admission to the hospital. Necropsy showed tuberculous pneumonia involving the entire left lung. The thyroid gland showed no histologic evidence of toxic hyperplasia or iodine response, the appearance was that of a colloid goiter with fibrosis.

These cases lend some support to the possibility that the clinical picture of hyperthyroidism may be produced by the action of the tuberculotoxin in stimulating the thyroid gland without producing the structural changes characteristic of toxic goiter.

Our experience suggests that the coexistence of hyperthyroidism and pulmonary tuberculosis is commoner than has generally been believed, at least in a metropolitan population (all our patients lived in or near Philadelphia). We could not obtain clear evidence from our patients' histories as to which of the diseases tended to appear first, although tuberculosis was not suspected in 15 of the 23 cases when the patient was first referred for treatment of hyperthyroidism. The progress of our patients definitely suggests that the relief of hyperthyroidism did not influence favorably the prognosis of the pulmonary lesion. Conversely, the presence of active tuberculosis seemed to impair slightly the prospect for complete cure of coexistent hyperthyroidism (table 5).

SUMMARY

The more important literature relating to various aspects of the relation between the thyroid gland and tuberculosis has been briefly reviewed.

The clinical incidence of pulmonary tuberculosis in hyperthyroidism and of hyperthyroidism in pulmonary tuberculosis at the Hospital of the University of Pennsylvania over a period of sixty-eight months is reported.

The changes observed in the thyroid gland at necropsy on 108 persons with pulmonary tuberculosis and the incidence of tuberculosis at necropsy on 18 thyrotoxic patients are reported

The significant data relating to 23 patients with associated hyperthyroidism and pulmonary tuberculosis are presented and discussed

CONCLUSIONS

Our series of cases is too small to warrant any generalizations, but our experience suggests the following conclusions

The administration of iodine to thyrotoxic patients with pulmonary tuberculosis does not tend to precipitate any immediate exacerbation or extension of the tuberculosis

An operation on the thyroid gland is usually well tolerated by patients with pulmonary tuberculosis

The coexistence of pulmonary tuberculosis does not impair materially the prospect for the successful treatment (irradiation or operation) of hyperthyroidism

The relief of hyperthyroidism does not seem to influence favorably the prognosis for patients with associated active pulmonary tuberculosis

The clinical picture of hyperthyroidism, without characteristic structural changes in the thyroid gland, may occur in patients with active pulmonary tuberculosis

Dr E B Krumbhaar, of the Department of Pathology, the University of Pennsylvania School of Medicine, gave us permission to review the necropsy records Dr Thomas Fitz-Hugh Jr gave us permission to include 1 of his private patients in our series

PROLONGED MENINGOCOCCEMIA

REPORT OF THREE CASES

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The recognition of meningococcic septicemia is an achievement of the twentieth century. Although the causative organism of meningitis was recognized and described by Weichselbaum in 1887, it was not until Gwyn's¹ report in 1899 that the meningococcus was demonstrated in the blood. Since the beginning of this century the American literature has contained many reports of extrameningeal types of meningococcic infection, but there have been relatively few reports of prolonged meningococcemia.

In the early part of this century it was believed by many that meningococcic septicemia if it occurs at all only follows an attack of meningitis and that the eruption so frequently seen in cases of meningitis is caused by a circulating toxin. Experience during and since the World War has led to acceptance of the belief so ably set forth by W. W. Herrick² in 1919. He divided meningococcic sepsis into three stages. The first stage is one of local infection of the upper respiratory passages, lasting two days to six weeks. The second is one of general invasion of the blood stream, usually lasting forty-eight hours. Finally, there is the stage of metastatic localization of the organisms in the meninges or other organs as the third and last stage.

It has now become a well established fact that an infection caused by the meningococcus may reach the second stage and go no farther, and, indeed, there are now enough examples to demonstrate that prolonged meningococcic infection of the blood is a definite disease entity. The time-honored tendency to associate all meningococcic infections with "epidemic cerebrospinal meningitis" has naturally obscured this group

From the Medical Service of the Walter Reed General Hospital

1 Gwyn, N. B. A Case of General Infection by the *Diplococcus Intracellularis* Weichselbaum, *Bull. Johns Hopkins Hosp.* **10** 112-113 (June) 1899.

2 Herrick, W. W. Extrameningeal Meningococcus Infections, *Arch. Int. Med.* **23** 409-418 (April) 1919.

of extrameningeal infections. It is therefore urged that this term be abandoned in favor of the more generically correct term meningococcic meningitis.

The first case of prolonged meningococcemia was reported by Solomon,³ in Germany, in 1902. The following summary was taken from the discussions by Bovaird⁴ and Bray.⁵ This patient, a woman of 32 years, suffered for two months with intermittent chills, fever, rash, myalgia and arthralgia. Culture of the blood yielded meningococci, and it was not until two months after the onset that meningitis supervened. She recovered after an illness of four months.

REPORT OF CASES

CASE 1—T. M., a private, stationed at Fort Mason, Calif., was admitted to the Letterman Hospital on June 2, 1929, with the complaint of sudden onset of chills, vertigo, headache and pain in the abdomen. He had a temperature of 103 F. Examination revealed a scanty macular rash over the abdomen and extremities and moderate leukocytosis. Six days after his admission to the hospital culture of the blood yielded meningococci. From June 12 to 23 a total of 500 cc of antimeningococcus serum was given intravenously in ten injections of 50 cc each, but the patient's condition remained essentially unchanged and the fever persisted, being of an intermittent septic type. Thirty-three days after the onset, the patient suffered from intense headache, nausea and vomiting. He had definite signs of meningitis, and the spinal fluid contained 6,000 white blood cells, with 80 per cent polymorphonuclears. An additional 130 cc of antimeningococcus serum was given intrathecally, and the patient made a complete recovery.

CASE 2—E. H. P., a private, stationed at Fort Howard, Md., suddenly became ill on May 3, 1936, with recurring attacks of chills and fever. He was admitted to the station hospital on May 10. For six weeks he had an intermittent fever (the temperature ranging from normal to 103 and 104 F) which recurred every three or four days. During this time he noted frequent severe attacks of arthralgia and occasionally "spots" on his legs, but between the paroxysms of fever he was free from symptoms. Forty-three days after the onset of the illness, during one of the paroxysms of fever, he experienced an intense headache and became very ill. He was admitted to the Walter Reed Hospital on the same day, and it was immediately decided that he had meningitis. Lumbar puncture revealed cloudy fluid, a high leukocyte count and intracellular germ-negative diplococci on a smear. He was given 100 cc of antimeningococcus serum intravenously and 240 cc intraspinally. He made a complete recovery after an illness of seven weeks.

CASE 3—M. W. T., a captain aged 33, was admitted to the Walter Reed Hospital on April 2, 1936, the diagnosis which was made before transfer being acute rheumatic fever. The past history was noncontributory except for the fact that one month prior to his admission to the hospital his left thumb had been bitten by his

3 Solomon, H. Ueber Meningokokkenseptikämie, *Klin. Wchnschr.* **39** 1045, 1902.

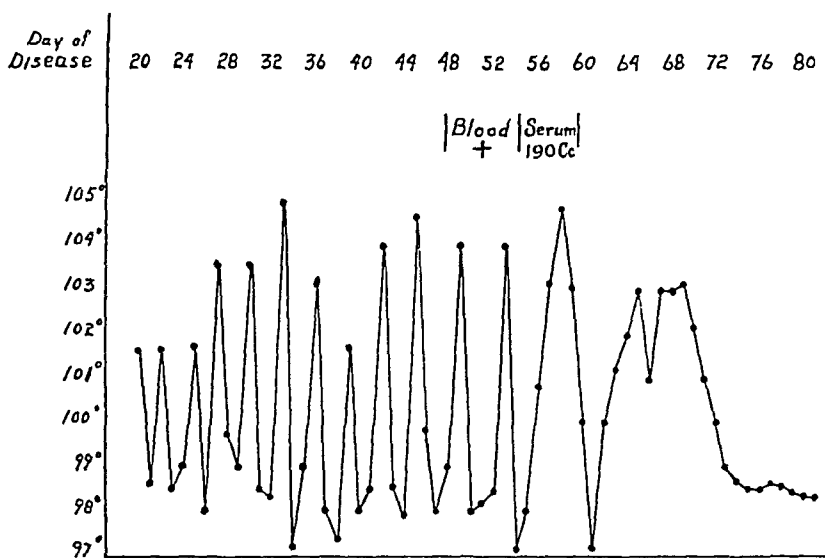
4 Bovaird, David, Jr. Meningococcus Septicemia with Sterile Cerebrospinal Fluid, Iridocyclitis, Flexner's Serum, Recovery, *Arch. Int. Med.* **3** 267-278 (April) 1909.

5 Bray, H. A. Chronic Meningococcus Septicemia Associated with Pulmonary Tuberculosis, *Arch. Int. Med.* **16** 487-502 (Sept.) 1915.

small dog This lesion became infected and suppurated, but no swelling of the regional lymph nodes or general systemic reaction was noted

Present Illness—Twelve days prior to admission to the hospital the patient did not feel well The following day he noted the onset of generalized aches and pains, with slight headache and sore throat These symptoms subsided for three days, only to reappear and persist for seven days prior to his admission to the hospital During the recrudescence the temperature rose to 103 or 104 F once a day, and he had severe pains in the elbows, knees, shins, calves and ankles A rash appeared which consisted of slightly swollen areas on the arms, chest and legs

Physical Examination—The patient was brought into the hospital on a litter The temperature was 100 F, the pulse rate 100 and the respiratory rate 26 There was a generalized erythematous maculopapular rash over the arms, chest and legs The lesions ranged from the size of a pinpoint to 1 or 1.5 cm in diameter A few of them had yellow raised centers On the dorsum of the left thumb was an



Temperature curve for third patient

exfoliating lesion about 3 cm in diameter which was not suppurating There was no general glandular enlargement, and the circulatory system was normal The blood pressure was 120 systolic and 80 diastolic No cardiac murmurs were noted The lungs were clear to percussion and auscultation The abdomen was flat and soft, and the spleen was not palpable Neurologic examination revealed no abnormality

Laboratory Data—The blood always showed a normal red cell count The white cell count ranged from 10,000 to 21,000 The Wassermann and Kahn reactions were negative Roentgenograms of the chest, with cardiac measurements were normal Cultures of the blood made before May 8 were sterile, and repeated agglutination for the typhoid, paratyphoid, brucella, pasteurella and proteus groups gave negative results Six intensive examinations of the blood revealed no malarial organisms The possibility of relapsing fever or rat-bite fever was ruled out on the basis of animal inoculation On May 5 the blood serum was found to agglutinate type II meningococci in a titer of 1:160 On May 8 blood collected by Col Arthur P Hitchins of the Army Medical School, and planted on Kracke's

culture medium of buffered tissue fluid⁶ yielded the meningococcus. One subsequent culture of the blood was also positive for type II meningococcus.

Course—During the first seven weeks of his illness the course was characterized by paroxysms of fever, occurring every third or fourth day, accompanied with marked prostration, myalgia, arthralgia, headache and rash. The severity of these attacks gradually increased, and occasionally the temperature reached 104 or 105 F. It was during this stage that several diagnoses were considered, including those of acute rheumatic fever, endocarditis due to *Streptococcus viridans*, malaria, undulant fever, rat-bite fever and finally meningococemia.

On the fifty-fourth day of the illness it was learned that the patient had had injections of therapeutic horse serum on two previous occasions. He was found to be moderately sensitive, but, despite this, it was thought advisable to administer serum. A total of 190 cc of a polyvalent antimeningococcus serum was given parenterally in divided doses. After severe serum sickness, the patient recovered without complications or sequelae. The duration of his illness was seventy days.

COMMENT

From the reports of thirty-three cases collected from the American literature the average age was found to be 27.7 years, with extremes of 8.5 and 48 years. Twenty-three cases occurred in males.

Incidence of Various Signs and Symptoms in Thirty-Three Cases of Meningococemia

	Cases		Cases
Rash	30	Sweating	11
Intermittent fever	26	Vomiting	6
Arthralgia	23	Sore throat	5
Chills	21	Epistaxis	2
Headache	17	Herpes	2
Myalgia	12	Bronchitis	2

It was noted that the onset in the majority of these cases was described as sudden—within one or two days—and was characterized by headache, chills, fever, rash and aches and pains in the muscles and joints. Occasionally bronchitis, tonsillitis and pharyngitis were noticed. One case reported by Morgan⁷ shortly followed the extraction of a tooth. Though one might expect to find sinusitis as a common symptom, definite sinus infection was demonstrated in only one case in this series.

The pains in the joints and muscles were such prominent features that the usual initial diagnosis was acute rheumatic fever. During the first week, however, it was commonly noted that the patients exhibited an intermittent type of fever, similar in many respects to either tertian or quartan malarial fever (chart). It was frequently so suggestive that

⁶ Simmons, J. S. Laboratory Methods of the United States Army. Philadelphia, Lea & Febiger, 1935.

⁷ Morgan, Hugh J. Chronic Meningococcus Septicemia. Bull. Johns Hopkins Hosp. 32: 245-254 (Aug.) 1921.

after a course of salicylates, quinine was often given in the face of an inability to demonstrate plasmodia in the blood. This likeness to the paludal types of fever has been especially commented on by Rolleston,⁸ Dock,⁹ Vesell and Barsky¹⁰ and Bloedorn.¹¹

The rash, recorded in thirty cases, consisted of multiform erythematous lesions, ranging from the size of a pinhead to 1.5 to 2 cm in diameter. Occasionally, white raised centers were noted, but the most characteristic lesions were small pink papules with red centers, usually located on the arms, legs and chest. These lesions tended to come in crops just before or just after the fastigium of the paroxysm of fever. Good reproductions of these lesions can be found in the articles by Richter,¹² Harrison and Abernethy¹³ and Brown.¹⁴

Certain other features of this type of septicemia deserve comment. The progressive secondary anemia that is so characteristic of other types of septicemia was rarely found. Severe cachexia was not the rule. Indeed, the patient often waited weeks before seeking medical aid because of the feeling of well-being between the paroxysms. Enlargement of the spleen, clubbing of the fingers, pallor of the skin, perisplenitis and hematuria, so characteristically found in the type of endocarditis due to *St. viridans*, were infrequently encountered in meningococcemia. Jaundice was consistently not mentioned in the case reports of this disease. In our cases there was no disproportion between the temperature and the pulse rate. The average duration of the disease was eleven and nine-tenths weeks, with extremes of five and thirty-two weeks. There were three deaths in the thirty-three cases in this series, making a mortality of 9.1 per cent. Two of the patients died after the onset of meningitis.¹⁵ The third case, though permission for necropsy was not granted, was probably complicated by endocarditis.¹⁶ A fourth patient died of nephritis five months after recovery from meningococcemia.¹³

8 Rolleston, Humphry. Lumleian Lectures on Cerebrospinal Fever, *Lancet* **1** 541-549 (April 5) 1919.

9 Dock, William. Intermittent Fever of Seven Months' Duration Due to Meningococcemia, *J A M A* **83** 31-33 (July 5) 1924.

10 Vesell, Harry, and Barsky, Joseph. Chronic Meningococcus Septicemia, *Am J M Sc* **179** 589-599 (May) 1930.

11 Bloedorn, W. A. Meningococcus Septicemia, *Am J M Sc* **162** 881-891 (Dec) 1921.

12 Richter, Arthur B. Meningococcemia. Report of Two Cases with Recovery, *J A M A* **102** 2012-2015 (June 16) 1934.

13 Harrison, F. F., and Abernethy, T. J. Chronic Meningococcemia, *Clin Misc*, Mary I. Bassett Hosp **1** 3-15, 1934.

14 Brown, C. L. The Skin Lesions in Meningococcus Septicemia, *Am J Dis Child* **27** 598-602 (June) 1937.

15 Dock,⁹ Vesell and Barsky.¹⁰

16 Hennell, Herman, and Wiener, Herbert J. Report of a Case of Chronic Meningococcemia, *M J & Rec* **131** 292-295 (March 19) 1930.

Much attention has been focused on the heart, and several cases of systolic murmurs were reported,¹⁷ a few cases in association with cardiac enlargement¹⁸ Whether these findings are signs of real endocarditis or the effects of fever and toxemia cannot be settled here, though it should be pointed out that in the cases of meningococcic sepsis in which there are signs of congestive failure and cardiac incompetency, the mortality is high and in these cases definite vegetative endocarditis is always demonstrated at necropsy The reader is urged to refer to the illustrated articles by Rhoads,¹⁹ Bancker,²⁰ Gwyn²¹ and Hyland²² for further study of this phase of the subject The dividing line between prolonged meningococcemia and meningococcic endocarditis is not an easy one to draw, and an overlapping of the cases cannot be avoided There have been, however, as many as fourteen cases in which the clinical picture was primarily one of cardiac failure and in which the characteristic symptoms of prolonged septicemia were absent For example, Cecil and Soper²³ reported a case in which the prolonged intermittent character of meningococcemia was absent There was no rash until shortly before death, and the fever was of the high sustained type The duration of illness in this case was twenty-four days, and at necropsy definite endocarditis was demonstrated Warfield²⁴ reported the case of a 32 year old Negro who had been sick for one week before coming to the hospital The initial symptoms consisted of headache, chills, cough and delirium A palpable precordial thrill, a systolic murmur and an irregular pulse were noted when he was admitted There was no rash or meningitis After an illness of five weeks he died, and the necropsy showed vegetative endocarditis A case of this type is primarily endocarditis and should not be included in a series of cases of prolonged meningococcemia

17 (a) Clark, Fred B Chronic Meningococcemia, *California & West Med* **34** 361-364 (May) 1931 (b) Master Arthur M Meningococcemia with Endocarditis, *J A M A* **96** 164-166 (Jan 17) 1931 (c) Bray⁵ Dock⁹ Hennell and Wiener¹⁶

18 Hennell and Wiener¹⁶ Master^{17b}

19 Rhoads, C P Vegetative Endocarditis Due to the Meningococcus, *Am J Path* **3** 623-629 (Nov) 1927

20 Bancker, Evert A Meningococcus Endocarditis, *J M A Georgia* **19** 480-485 (Nov) 1930

21 Gwyn, N B Subacute Meningococcal Endocarditis, *Arch Int Med* **48** 1110-1117 (Dec) 1931

22 Hyland, C M Meningococcus Endocarditis, *J A M A* **92** 1412 (April 27) 1929

23 Cecil, Russell L, and Soper, Willard B Meningococcus Endocarditis, with Septicemia, *Arch Int Med* **8** 1-16 (July) 1911

24 Warfield Louis M Acute Ulcerative Endocarditis Caused by the Meningococcus (Weichselbaum), *Univ Pennsylvania M Bull* **16** 180-182 (July-Aug) 1903

There have been, however, at least four cases of prolonged meningococcemia in which there was evidence strongly suggesting the complication of acute endocarditis. The first case, reported by Hennell and Wiener,¹⁶ was that of a man of 40 who gave a history of four weeks of intermittent attacks of chills, fever, sweats and rash, with the feeling of well-being between attacks. During the fourth week the rash, chills and sweats disappeared, and he became weak and was confined to bed. From then until death occurred the temperature remained continuously high. There were undoubted signs of endocarditis of the aortic and mitral valves, and even though permission for necropsy was not granted it can be considered that this was a case of prolonged meningococcemia complicated by acute endocarditis. Master^{17b} reported three cases in which there was presumptive evidence of acute endocarditis complicating prolonged meningococcemia. In these three cases recovery occurred after thorough treatment with serum. Consequently, absolute proof is lacking, but the data serve to emphasize the fact that there are a small group of borderline cases that reveal the relation of simple prolonged meningococcemia to endocarditis. They bear the same relation to each other that prolonged meningococcemia bears to meningococcal meningitis.

Headache was reported in seventeen of the cases and vomiting in six of the cases as the only symptom referable to the central nervous system that occurred prior to the onset of meningitis. When meningitis supervened it was always heralded by signs of severe meningeal irritation and increased intracranial pressure. Nineteen of the patients (57.5 per cent) of this series did not have meningitis. In fourteen patients (42.5 per cent) meningitis developed, in three patients meningitis developed before the prolonged septicemia set in²⁵ in ten it developed late in the course of the septicemia and in one case there were two separate attacks.²⁶ Hemiplegia was a complication in Conklin's case.²⁷

Anemia was not a prominent feature except in the three cases complicated by nephritis and the one complicated by Banti's splenic anemia.²⁸ A leukocyte count ranging from 10 000 to 20 000 with an increase of polymorphonuclears was the usual finding though in the one case of

25 (a) Mancu Kenneth F. Observations on the Presence of Meningococcus in the Blood. *J Infect Dis* **23** 470-474 1918. (b) Seeley Sam F. Meningococcal Septicemia. *Mil Surgeon* **71** 309-313 (Oct) 1932. (c) Lemann I I, and Teasley H E. Meningococcemia for Eight Months Following Meningitis. Recovery. *New Orleans M & S J* **83** 448-453 (Jan) 1931.

26 Graves, W R, Dulaney Anna Dean and Mickelson I D. Chronic Meningococcemia. *J A M A* **92** 1923-1925 (June 8) 1929.

27 Conklin, Coursen B. Meningococcemia, *M Ann District of Columbia* **4** 313-315 (Dec) 1935.

28 Binns, James F, and Fothergill, Leroy D. Chronic Meningococcus Septicemia, *New England J Med* **205** 536-539 (Sept 10) 1931.

Banti's disease leukopenia was present. It is interesting to note that after this patient recovered from the meningococcemia, splenectomy was accomplished, with consequent improvement of the patient.

The most important single factor in the diagnosis of meningococcemia is to have the disease in mind. In a few cases the condition was diagnosed within the first few days, but in the majority of cases three to five weeks elapsed before a diagnosis was made. It does not need to be emphasized that culture of the blood is the most useful of all laboratory procedures in making a diagnosis, but it must be stressed that the usual beef broth and agar are poor mediums in which to grow the meningococcus from the blood.²⁹ In order to insure prompt growth the medium should be especially enriched with ascitic fluid or blood serum. Negative results of culture, even with enriched mediums, do not exclude meningococcemia, because several cases have been reported in which especially enriched mediums were used and positive results were not obtained until after the fifteenth day.³⁰ In case 3 of our series the first positive evidence of meningococcemia was obtained from blood agglutination against stock meningococci. This procedure should be carried out whenever feasible as it may prove to give valuable confirmative evidence. After the organism has been recovered from the blood it should be differentiated from the gonococcus by the sugar fermentation test and then agglutinated by the different commercial polyvalent antimeningococcus serums in various dilutions in order to determine the best serum to use in treatment. According to Herrick,² the commercial serum should agglutinate in dilutions of 1:50 or greater if it is to be effective at all. More attention should be paid to the differentiation of the various types of meningococci obtainable from patients with meningococcic infections because it is not unreasonable to suppose that the same situation is present here as obtains in the field of pneumococcic infections.

The most effective treatment of this disease is the use of the proper antimeningococcus serum. It is worthy of note that thirty of the thirty-three patients in this series received antimeningococcic serum, one of the three who did not receive serum died. Severe anaphylactic reactions were reported in three cases.³¹ The majority of the authors reported prompt improvement after the use of a potent serum. Poor results can usually be accounted for by impotent serum or serum with too low an agglutination titer for the causative organism. Type II and type IV

29 Beaslack, F. W., and others. Cultivation of the *Meningococcus Intracellularis* (Weichselbaum) from the Blood, *J. A. M. A.* **70**: 684-686 (March 9) 1918.

30 Morgan, J. Dock.⁹

31 Marlow, F. W. Meningococcemia. Report of Case with Recovery, *J. A. M. A.* **92**: 619-621 (Feb. 23) 1929. Macy²⁵; Seeley^{23b}.

meningococci are organisms with a relatively low virulence, in contrast to type I and type III meningococci, and usually cause prolonged and chronic infection. The various commercial serums are made to be especially effective in meningococcic infection caused by the more virulent types, and they vary greatly in their potency for the less virulent types. It is therefore of prime importance that care be exercised in selecting the serum to be used. The amount of serum necessary to bring about a cure varies markedly from case to case, but assuming that a potent serum is being used, quantities from 30 to 500 cc have been found effective. In case serum proves to be ineffectual, antitoxin should be tried. Vaccine has been employed in a few cases but without striking results. Immunotransfusion³² seems to be a rational form of therapy, but, again, results are not so gratifying as one would expect. Abscess fixation, nonspecific protein³³ and numerous intravenous antiseptics have all been employed but with only a small measure of success. The recently introduced chemotherapeutic agent sulfanilamide (para-aminobenzenesulfonamide) may prove to be very useful in the treatment of meningococcemia. It should be employed in combination with a potent serum, because there is evidence to support the view that this drug is more effective against certain strains of meningococci than others³⁴.

SUMMARY

Three cases of prolonged meningococcemia are reported the third being described in detail.

Reports of thirty additional cases collected from the American literature are analyzed and discussed.

Prolonged meningococcemia is a rare disease but should be kept in mind in making a diagnosis in all cases of septicemia in which the essential features are long-standing intermittent fever, cutaneous rash, arthralgia, myalgia, headache and the maintenance of a fair state of health.

An attempt should always be made to differentiate between prolonged meningococcemia and meningococcic endocarditis because of the difference in the prognosis in the two conditions.

The most effective form of treatment is found in the use of the proper antimeningococcus serum in conjunction with sulfanilamide.

32 Edmundson, Frank. Meningococcemia Without Meningeal Symptoms, *Hahneman Monthly* **67** 106-109 (Feb.) 1932.

33 Neergaard, Arthur E. Meningococcus Bacteremia, *M. Clin. North America* **9** 461-469 (Sept.) 1925.

34 Branham, Sara E., and Rosenthal, Sanford M. Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, *Pub. Health Rep.* **52** 685-695 (May 28) 1937.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1937

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NEW YORK

Previous reviews of the literature dealing with diseases of the liver and biliary tract¹ have made no special reference to textbooks and monographs dealing with the general subject of disease of the liver. At present this policy is abandoned to report the appearance during 1937 of the new textbook on hepatic disease by Eppinger². The book has been divided into two sections—general and special pathology, and the subject has been discussed in truly encyclopedic fashion. For the greater part the views expressed are those generally current, though these have been presented in the light of the author's personal experience in both the experimental laboratory and the medical clinic. This point of view has stressed the work of the German laboratories, but other important contributions have not been overlooked. This volume of 800 pages therefore will take its place as one of the standard reference books for advanced students in this field of medicine. Its cost, unfortunately, will prevent its wider use in this country.

No attempt will be made to review the book in detail or to discuss various controversial points. When the greater frequency of diseases of the gallbladder and bile ducts relative to that of hepatic disease is

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1 Greene, C H , Bercovitz, Z , and Hanssen, E C. Liver and Biliary Tract. Review of the Literature of 1933 and 1934, *Arch Int Med* **55** 681 (April) 1935. Greene, C H. Liver and Biliary Tract. A Review of Certain Recent Contributions, *ibid* **57** 1039 (May) 1936. Greene, C H , Handelsman, M B , and Babey, A M. Liver and Biliary Tract. A Review for 1936, *ibid* **59** 724 (April) 1937.

2 Eppinger, H. *Die Leberkrankheiten. Allgemeine und spezielle Pathologie und Therapie der Leber*, Vienna, Julius Springer, 1937.

considered, it is perhaps unfortunate that the former diseases were not given a proportionate emphasis. Some of this was unavoidable, for while the book was published in 1937, the mechanical aspects of book making consume much time. No references to the American literature later than 1934 were noted, and as pointed out in these reviews many important contributions have been reported in the past four years.

PIGMENT METABOLISM IN RELATION TO JAUNDICE AND HEPATIC DISEASE

Bilirubin—Jaundice of itself is evidence of disturbance in the formation or in the excretion of bile. The value of the determination of the bile pigment content of the blood serum (1) in revealing the presence of latent icterus, (2) as an index of the degree of retention of pigment and (3) as a measure of the changes during the course of the disease has been thoroughly demonstrated. Various methods have been used for this study of the pigment in the serum, the simplest and most popular being the icterus index and the quantitative van den Bergh reaction.

It is generally accepted that bilirubin is formed by the decomposition of hemoglobin. This destruction of blood pigment takes place primarily in the cells of the reticuloendothelial system rather than in the parenchymal cells of the liver. The Kupffer cells of the liver, which are part of the reticuloendothelial system, thus take part in the formation of bile pigment, but considerable quantities of bilirubin are formed in the spleen and bone marrow as well. It has been argued that the liver acts as an excretory organ with respect to bilirubin, just as the kidney does with respect to urea. This analogy may not be entirely accurate, for the bile pigment apparently is modified slightly during the process of excretion. The pigment which is normally present in the blood serum in small amount gives an indirect van den Bergh reaction. After the bilirubin has passed through the hepatic cells and entered the bile, the van den Bergh reaction becomes direct. There has been a great deal of controversy regarding the reason for this change in the character of the bilirubin. Some investigators insist that there are distinct chemical differences, and Harrison³ suggested the use of the terms hemobilirubin and cholebilirubin to designate the two types of pigment. Regardless of the final explanation of the two types of van den Bergh reaction, the finding of an indirect reaction in the presence of clinical jaundice empirically but conclusively demonstrates that the jaundice is hemolytic in origin. The so-called delayed

3 Harrison, G. A. *Chemical Methods in Clinical Medicine. Their Application and Interpretation, with the Technique of the Simple Tests.* London: J. & A. Churchill, 1930.

and diphasic types of reaction apparently are quantitative modifications of the direct reaction and are valueless for the differentiation of hepatogenous from obstructive types of jaundice

Hemobilirubin is present in normal blood serum and is increased in amount in cases of hemolytic jaundice. It gives the indirect van den Bergh reaction and is readily extracted by chloroform. The cholebilirubin present in bile and in the blood serum in cases of hepatic or of obstructive jaundice gives the direct van den Bergh reaction and is not extracted by chloroform. Hemobilirubin has been described as bound by protein and therefore nondialyzable, in contrast to cholebilirubin, which is free and dialyzable. We have not found this to be a satisfactory method of separation of the two fractions, and similar results have been reported by Gregory and Andersch⁴. The differences in solubility in chloroform permit an apparent separation of the two types of pigment in the serum. Varela and Esculies,⁵ Kerppola,⁶ and Bengolea, Velasco-Suárez and Raices⁷ have reported quantitative studies of the two types of bilirubin in the blood of jaundiced patients. In jaundice there may be an increase in the amount of both the water-soluble and the chloroform-soluble bilirubin in the serum, but the relative proportion of the two is not constant, they seem to vary independently (fig 1).

If further studies substantiate the separate identity of the two forms of bilirubin and the validity of this method of separation, it may then be possible to assay the relative importance of the two factors, that is, icterus by retention and icterus by resorption which are the basis of the classification of jaundice proposed by Rich⁸. The results indicate that in most cases of jaundice the hemobilirubin fraction is increased with the appearance of cholebilirubin in the serum and so suggest that hemolytic processes play a larger role in the pathogenesis of jaundice than is usually accepted.

4 Gregory, R. L., and Andersch, M. The Filterability of Bilirubin in Obstructive Jaundice, *J. Lab. & Clin. Med.* **22** 1111, 1937.

5 Varela, B., and Esculies, J. Nouvelle methode pour la séparation et le dosage des deux bilirubines (directes et indirectes) du serum sanguin, *Compt. rend. Soc. de biol.* **107** 884, 1931. Varela, B., Recorte, P., and Esculies, J. Méthode simplifiée pour la separation et le dosage isolé des deux bilirubines, directe et indirecte, du serum sanguin dans les ictères, *ibid.* **108** 1009, 1931.

6 Kerppola, W. Extraction Method for the Quantitative Determination of Bilirubin in Different Body-Fluids, *Acta med. Scandinav.*, 1932, supp. 50, pp 277-280.

7 Bengolea, A. J., Velasco-Suarez, C., and Raices, A. E. El dosage de la bilirubina directa et indirecta en el suero sanguineo. Su importancia en cirugía hepato biliar, *Prensa med. argent.* **23** 85, 1936.

8 Rich, A. R. The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47** 338, 1930.

Urobilin and Urobilmogen—The early investigations of Friedrich von Mülle⁹ first established the importance of urobilinuria as evidence of a disturbance in hepatic function. The clinical value of qualitative or semiquantitative tests for urobilin as urobilmogen in the urine and stools has been summarized in such reports as those of Wilbur and Addis¹⁰ Wallace and Diamond,¹¹ White¹² and Eppinger,¹³ and

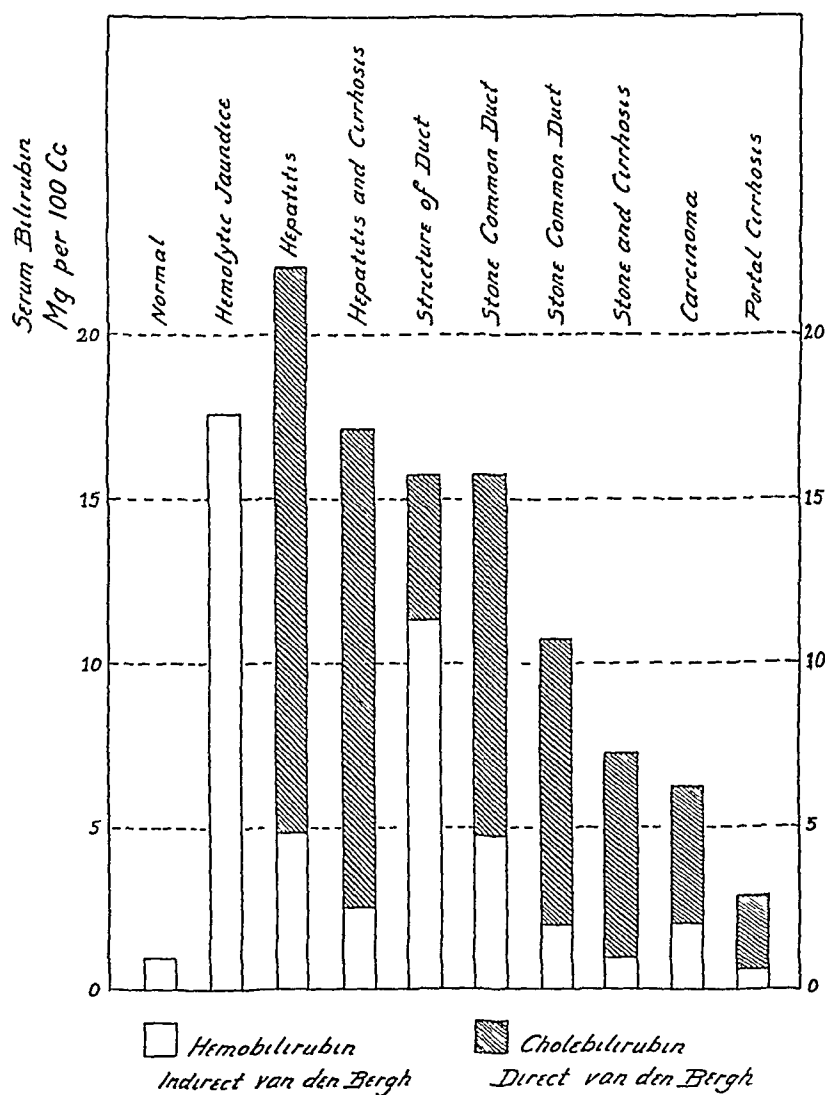


Fig 1—The distribution of the two types of bilirubin in the serum in an illustrative series of cases of jaundice (authors' data)

⁹ von Muller, F. Ueber Ikterus, Jahresb d schles Gesellsch f vaterl Kult 70 1, 1893

¹⁰ Wilbur, R. L., and Addis, T. Urobilin. Its Clinical Significance, Arch Int Med 13 235 (Feb) 1914

many otherwise controversial questions have been settled by the experimental studies of Elman and McMaster¹⁴ These various studies have demonstrated that urobilinogen normally is formed in the intestine by the bacterial decomposition of the bile pigments Some of the urobilinogen is absorbed and is carried by the portal blood stream to the liver A portion possibly may be used in the synthesis of hemoglobin, but the major part is excreted in the bile If bile is excluded from the intestine, either because of the presence of complete biliary obstruction or because of a biliary fistula, the formation of urobilinogen ceases, and this pigment disappears from the bile, stool and urine The liver normally removes nearly all the urobilinogen from the portal blood, and only small amounts escape into the systemic circulation to appear in the urine

The reserve capacity of the liver for the excretion of urobilinogen is slight, and slight degrees of hepatic injury or damage therefore suffice to permit the escape of urobilinogen into the general circulation and its appearance in the urine This accounts for the frequency of urobilinogenuria in cases of jaundice due to hepatitis or to stones in which the obstruction to the common duct is not complete Positive results of tests are also the rule in portal cirrhosis in which hepatic damage is present and in which the presence of collateral venous channels makes it possible for urobilinogen to pass from the portal to the systemic circulation without passing through the liver

Urobilinogenuria also is present in blood dyscrasias, such as hemolytic jaundice or pernicious anemia, and in pneumonia, pulmonary infarction, hemorrhage and other conditions in which an increased destruction of hemoglobin and the excretion of an increased amount of pigment in the bile occurs More urobilinogen is formed in the intestine, and the consequent flooding of the liver is assumed to explain the urobilinogenuria Whether all the urobilinogenuria in such cases can be explained on this basis or whether an additional element of

11 Wallace, G B, and Diamond, J S Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch Int Med* **35** 698 (June) 1925

12 White, F W The Galactose-Tolerance and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, *Tr A Am Physicians* **50** 111, 1935, *Am J Digest Dis & Nutrition* **4** 315, 1937

13 Eppinger, H Die hepato-lienalen Erkrankungen, Berlin, Julius Springer, 1920

14 Elman, R, and McMaster, P D Studies on Urobilin Physiology and Pathology I The Quantitative Determination of Urobilin, *J Exper Med* **41** 503, 1925, II Derivation of Urobilin, Relation of Bile to the Presence of Urobilin in the Body, *ibid* **41** 513, 1925, III Absorption of Pigments of Biliary Derivation from the Intestine, *ibid* **41** 719, 1925, IV Urobilin and the Damaged Liver, *ibid* **42** 99, 1925, V The Relation Between Urobilin and Conditions Involving Increased Red Cell Destruction, *ibid* **42** 619, 1925, VI The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, *ibid* **43** 753, 1926

hepatic damage, perhaps produced by the associated anemia, must be assumed is still open to question

In the great majority of cases the presence of urobilinogenuria is evidence of the presence of bile in the intestinal tract. Even with complete biliary obstruction, traces of urobilinogen may be formed from bile-stained epithelial cells in the intestine. Infection of the biliary tract may also give rise to a local formation of urobilinogen. Such cases are infrequent, and these modes of formation of urobilinogen are of little clinical significance.

The early investigation of urobilinuria demonstrated the fluctuations observed in the study of casual specimens and emphasized the importance of quantitative determinations of the daily excretion in the urine.

The Daily Excretion of Urobilinogen in Health and in Disease (Watson)

	Number of Cases	Urobilin Excretion Mg per Day	
		Urine	Feces
Normal condition	26	0.4	40-280
Chronic infection	5	0.1	0-100
Febrile condition	11	0.38	100-300
Obstructive Jaundice			
Uncomplicated cholelithiasis	21	0.6	10-250
Stones with complications	20	4.50	10-250
Neoplastic disease	18	0-0.3	0-5
Diffuse hepatitis			
Acute catarrhal jaundice	11	4-200	10-300
Diffuse hepatitis with jaundice	10	4-100	8-200
Diffuse hepatitis or cirrhosis with blood destruction	7	20-200	300-1,200
Diffuse hepatitis or cirrhosis without jaundice	8	4-100	50-135
Congestive heart failure with jaundice and ascites	11	0.50	30-260
Carcinoma of the liver without jaundice	6	0.25	
Familial or congenital hemolytic jaundice	10	1-10	300-1,800
Acquired hemolytic jaundice	3	10-300	300-2,500

and stool. Moderately satisfactory methods for such study were devised by Terwen¹⁵ and more recently by Watson¹⁶. The latter made a comprehensive study of the urobilinogen in the urine and stool both of normal subjects and of patients with disease of the liver and biliary tract.

Watson¹⁷ studied 26 normal subjects and found that the urobilinogen excreted in the urine varies from 0 to 4 mg per day, usually from

15 Terwen, A. J. L. Ueber ein neues Verfahren zur quantitativen Urobilin-Bestimmung im Harn und Stuhl, *Deutsches Arch. f. klin. Med.* **149**: 72, 1925.

16 Watson, C. J. Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am. J. Clin. Path.* **6**: 458, 1936.

17 Watson, C. J. Studies of Urobilinogen. II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch. Int. Med.* **59**: 196 (Feb.) 1937, III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid.* **59**: 206 (Feb.) 1937.

0.5 to 2 mg. The urobilinogen content of the feces varies from 40 to 280 mg. Mild infection, inanition or inactivity uncomplicated by jaundice or anemia, tends to lower the excretion of urobilinogen in the feces. Fever of any considerable degree tends to increase the amount of urobilinogen in the feces, but fever alone without jaundice does not increase the degree of urobilinuria.

One hundred and thirty-five patients with jaundice or hepatic disease were studied by Watson¹⁸. In obstructive jaundice due to cholecystitis or cholelithiasis without complications the excretion of urobilinogen in the urine or in the stool was only slightly increased if at all over the normal. Relief of the obstruction with subsidence of the jaundice, apparently was accompanied temporarily by a marked increase in the excretion of urobilinogen, particularly that in the urine. In contrast to the findings in obstruction due to calculus, which rarely was complete, were those in carcinomatous obstruction. The degree of obstruction in the latter case usually was complete, and this was signalled by the almost complete disappearance of urobilinogen from both urine and stool.

In cases of acute catarrhal jaundice there was a normal excretion of urobilinogen in the stool, but the amount excreted in the urine regularly was increased over the amount found in cases of uncomplicated jaundice with stone. Similar findings were observed in cases of chronic hepatitis or cirrhosis.

Cases of chronic hepatitis or cirrhosis which was accompanied by an increased destruction of blood were characterized by the presence of an increased amount of urobilinogen in the urine, but the increase in the output of urobilinogen in the stool was especially marked.

The content of urobilinogen in the feces usually was increased to a marked degree in cases of hemolytic jaundice. In such cases splenectomy resulted in a rapid decrease. The urobilinogen content of the urine, however, was only moderately increased and could not be correlated with the increased destruction of blood. Watson therefore concluded that the urobilinuria seen in hemolytic types of jaundice was not due to flooding or overloading of the liver with urobilinogen but was evidence of functional disturbance in the liver.

These data reported by Watson confirm and extend the previously reported views by showing that the presence of urobilinogen in feces or urine is dependent on the passage of bile through the common duct into the intestine. Transient obstruction may occur from stones or acute hepatitis but persistent complete obstruction nearly always is

18. Watson C. J. The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, *Arch. Int. Med.* **47**: 698 (May) 1931. Watson¹⁷.

due to neoplasm. The amount of urobilinogen in the stool appears to vary with the rate of destruction of blood and presumably, therefore, with the excretion of bile pigment. The excretion of urobilinogen in the urine is a measure of hepatic insufficiency which, however, may be variously produced. It is most frequent and marked in the presence of diffuse hepatic disease. It is not present in cases of cholelithiasis unless there are complications, such as infection or anemia. In hemolytic jaundice the urobilinuria when present was a measure of hepatic dysfunction from anemia or other causes rather than a "flooding" of the liver as a result of the increased destruction of blood.

The collection of specimens and the quantitative determination of the daily excretion of urobilinogen in the urine and stools constitute a laborious procedure, but Watson has amply demonstrated its great diagnostic significance.

Porphyrins and Porphyrin Metabolism—The urine and stool contain not only bile pigments and their derivatives but another series of pigments, the porphyrins. These are of great biologic interest, for, as described in a recent review of this subject by Hans Fischer,¹⁹ the respiratory pigments are porphyrin compounds. The hemoglobin of the red blood corpuscles and the myoglobin of muscles are compounds composed of a porphyrin ion and a protein. The chlorophyll of green plants is a porphyrin-magnesium compound. The brown pigment of egg shells,²⁰ the pigment (tuacin)⁻¹ in the feathers of one species of South African bird, the chlorocruorin⁻² found in rare species of worms and the cytochrome C²³ found in yeast cells²⁴ and in many species of animals and plants are all porphyrin compounds.

The chemical structure of the porphyrins has been elucidated as a result largely of the work of Hans Fischer and his pupils.¹⁹ They have shown that porphyrins are composed of four pyrrole nuclei united by four methene bridges to form the porphin ring. In the naturally

19 Fischer, H., and Orth, H. *Die Chemie des Pyrrols*, Leipzig, Akademische Verlagsgesellschaft m. b. H., 1937, vol. 2.

20 Fischer, H., and Kogl, F. *Zur Kenntnis der natürlichen Porphyrine*. IV. Ueber das Ooporphyrin, *Ztschr. f. physiol. Chem.* **131** 241, 1923. Fischer, H., and Lindner, F. XIV. Ueber Ooporphyrin und seine Ueberführung in den Ester des Hamins, *ibid.* **142** 141, 1925.

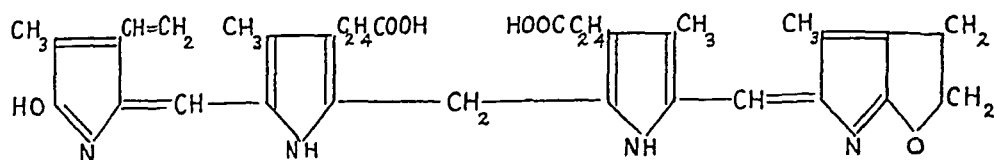
21 Fischer, H., and Hilger, J. *Zur Kenntnis der natürlichen Porphyrine*. Ueber das Vorkommen von Uroporphyrin in den Turakovögeln und den Nachweis von Koproporphyrin in der Hefe, *Ztschr. f. physiol. Chem.* **138** 59, 1924.

22 Fischer, H., and von Seemann, C. *Die Konstitution des Spirographishamins*, *Ztschr. f. physiol. Chem.* **242** 133, 1936.

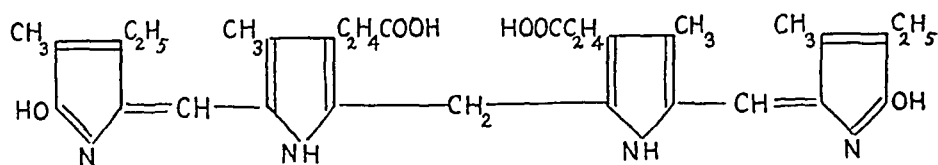
23 Zeile, K., and Reuter, F. *Ueber Cytochrom C*, *Ztschr. f. physiol. Chem.* **221** 101, 1933.

24 Fischer, H., and Hilmer, H. *Ueber Koproporphyrin-Synthese durch Hefe und ihre Beeinflussung*, *Ztschr. f. physiol. Chem.* **153** 167, 1926.

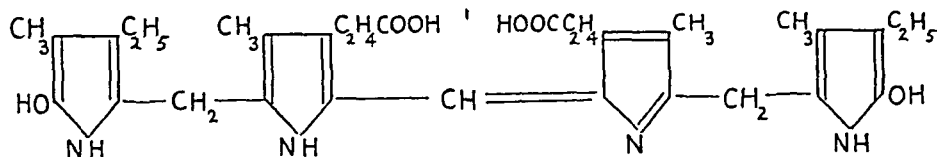
occurring porphyrins, various chemical groups have been substituted for the hydrogen atoms in the periphery of the porphin nucleus. By different arrangements of the substituting groups, a number of isomeric chemical compounds are possible. When the eight hydrogen atoms of the porphin nucleus are substituted, with four methyl and four



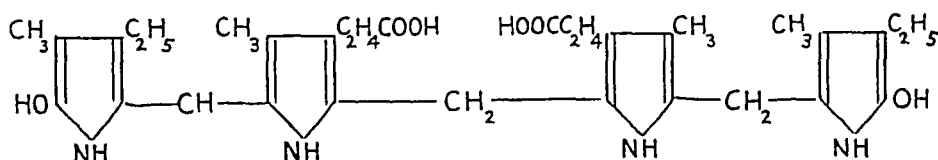
BILIRUBIN



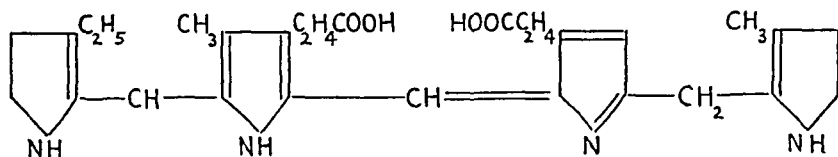
MESOBILIRUBIN



UROBILIN



MESOBILIRUBINOGEN - UROBILINOGEN



STERCIBILIN

Fig 2—The structural formulas of bilirubin, urobilinogen and related compounds (after Fischer)

ethyl groups, four isomeric etioporphyrins (types I to IV) are formed. They differ only in the arrangement of the substituent groups. The etioporphyrins do not occur naturally but are of importance as reference types, for the naturally occurring porphyrins may be classified as of similar construction to etioporphyrin of either type I or type III.

The respiratory pigments, hemoglobin,¹⁹ myoglobin,²⁵ cytochrome C,²³ chlorophyll and catalase,²⁶ are all compounds of type III porphyrin. The chemical formulas of some of these compounds are given in figures 2 to 4

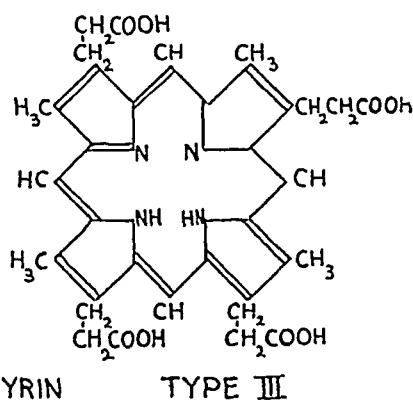
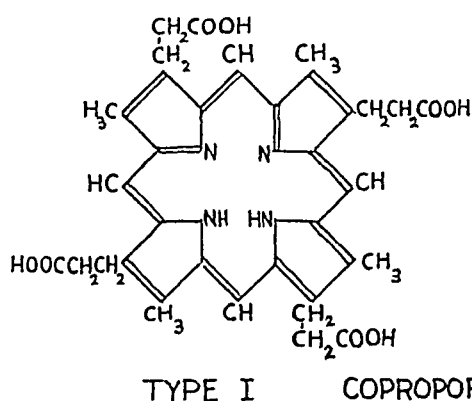
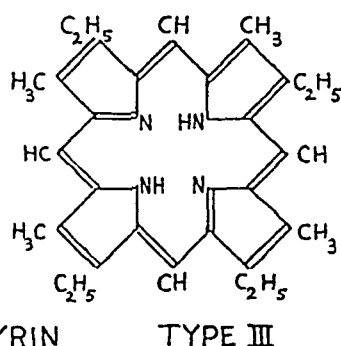
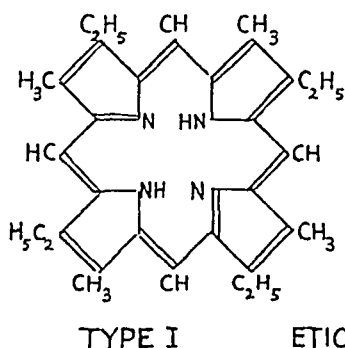
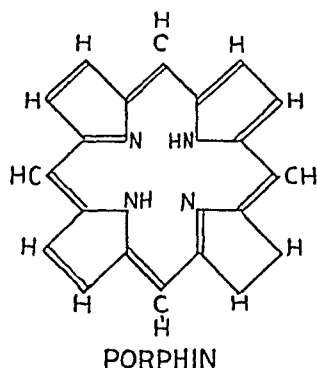
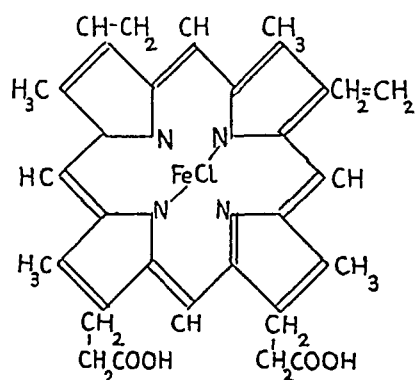


Fig 3—The structural formulas of porphin and related compounds (after Fischer)

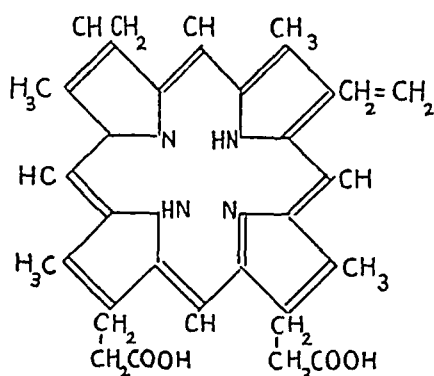
25 Schonheimer, R Ueber den roten Farbstoff der Herz- und Skelettmuskulatur, *Ztschr f physiol Chem* **180** 144, 1929

26 Stern, K G The Constitution of the Prosthetic Group of Catalase, *J Biol Chem* **112** 661, 1936

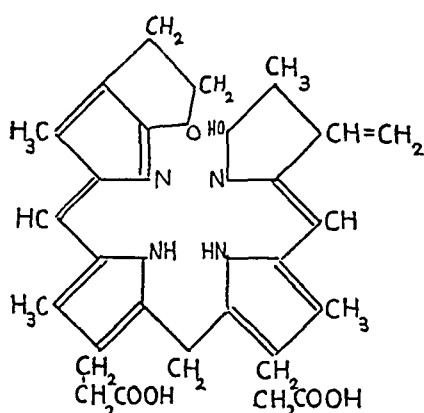
The early reports of Garrod²⁷ and Gunther²⁸ demonstrated the occurrence of clinical cases of porphyria, and Garrod emphasized that such cases represented a rare type of constitutional anomaly of pigment metabolism. Mason, Courville and Ziskind²⁹ summarized this literature and reported that congenital porphyria has been recorded in 27 cases and acute idiopathic porphyria in 48 cases. They also reported that about 100 cases of acute toxic porphyria have been recorded. Most



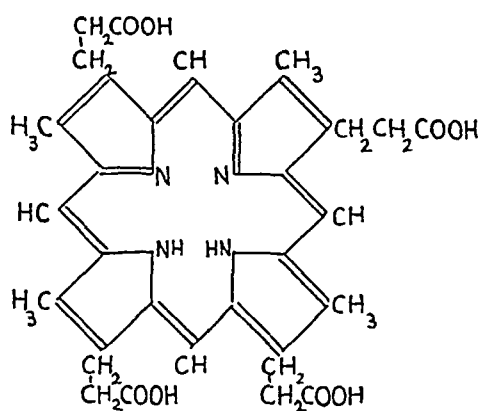
HEMIN



PROTOPORPHYRIN(IX) TYPE III



BILIRUBIN



COPROPORPHYRIN TYPE III

Fig 4—The structural formulas of various derivatives of type III porphyrin (after Fischer)

of these cases followed the long-continued abuse of sulfonmethane or sulfonethylmethane. Porphyrin metabolism has been summarized in

27 Garrod, A. E. Hematoporphyrin in Normal Urine, *J. Physiol.* **17** 349 1894, *Inborn Errors of Metabolism*, ed 2, London, Humphrey Milford, 1923, p. 136

28 Gunther, H. Die Bedeutung der Hamatoporphyrin in Physiologie und Pathologie, *Ergebn d. allg. Path. u. path. Anat.* **20** 609, 1922

29 Mason, V. R., Courville, C., and Ziskind, E. The Porphyrins in Human Disease, *Medicine* **12** 355, 1933

the reviews of Brugsch,³⁰ Canié,³¹ Vannotti³² and others³³ Porphyrina has been shown by Turner³⁴ to be present in the fox squirrel, in which the bones and urine normally are stained red by porphyrins

The excretion of porphyrins, however, is not limited to cases of porphyrina, for small amounts are excreted in the urine and stool both of normal persons and of patients suffering from a variety of pathologic conditions³⁵ The amount excreted usually is too small to produce clinical symptoms, though Beckh, Ellinger and Spies³⁶ have reported that in pellagra the excretion of porphyrin bears a rough relation to the intensity of the cutaneous lesions, and they have pointed out the similarity between the cutaneous symptoms of congenital porphyrinuria and those of pellagra An increased excretion of porphyrins does not always produce cutaneous symptoms, for most patients with acute or chronic porphyrinuria do not manifest this symptom³⁷ The porphyrins in the urine and stool of normal persons and of patients, including those with acute, chronic or congenital porphyrina, consist preponderantly of coproporphyrin type I, with traces of protoporphyrin type III and deuteroporphyrin type III Uroporphyrins of types I and

30 Brugsch, J T Die sekundären Störungen des Porphyrinstoffwechsels, *Ergebn d inn Med u Kinderh* **51** 86, 1936

31 Canié, C Die Porphyrine, Leipzig, Georg Thieme, 1936

32 Vannotti, A Porphyrin und Porphyrinrankheiten, Berlin, Julius Springer, 1937

33 Kammerer, H Biologie und Klinik der Porphyrine, *Verhandl d deutsch Gesellsch f inn Med* **45** 28, 1933 Fischer, H Ueber Hamin und Porphyrine, *ibid* **45** 7, 1933

34 Turner, W Studies on Porphyrina Observations on the Fox Squirrel, *J Biol Chem* **118** 519, 1937

35 (a) Fink, H, and Hoerbarger, W Isolierung von kristallisiertem Koproporphyrin I aus normalen menschlichen Urin, *Naturwissenschaften* **18** 292, 1934 (b) Watson, C J Concerning the Naturally Occurring Porphyrins I Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, *J Clin Investigation* **14** 106, 1935, II The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces in a Case of Familial Hemolytic Jaundice, *ibid* **14** 110, 1935, III Isolation of Coproporphyrin I from the Feces of Untreated Cases of Pernicious Anemia, *ibid* **14** 116, 1935, IV Urinary Porphyrins in Lead Poisoning as Contrasted with that Excreted Normally and in Other Diseases, *ibid* **15** 327, 1936, V Porphyrins of the Feces, *ibid* **16** 383, 1937 (c) Dobriner, K Urinary Porphyrins in Disease, *J Biol Chem* **113** 1, 1936, Porphyrin Excretion in the Feces in Normal and in Pathological Conditions, *ibid* **120** 115, 1937 (d) Vighani, E C, and Libowitzky, H Ueber Porphyrine im Harn und im Kot, *Klin Wchnschr* **16** 1243, 1937

36 Beckh, W, Ellinger, P, and Spies, T D Porphyrinuria in Pellagra, *Quart J Med* **6** 305, 1937

37 Waldenstrom, J Studien uber Porphyrie, *Acta med Scandinav*, 1937, supp 82, pp 1-254

III have also been recovered in cases of acute, chronic and congenital porphyria. Porphyrins of type I thus constitute the usual type found both normally and in the majority of pathologic conditions.

Coproporphyrin type III has been reported in the excreta in certain cases of lead poisoning,³⁸ in cases of aplastic anemia³⁹ and in cases of atrophic cirrhosis, pigment cirrhosis and melanocarcinoma of the liver.⁴⁰ The perfusion experiments of van den Bergh, Grotepass and Revers⁴¹ have demonstrated that the surviving liver is capable of converting protoporphyrin into coproporphyrin. Because of the hepatic damage in these cases it is possible that some of the protoporphyrin formed by the destruction of hemoglobin escapes conversion into bilirubin and may be converted into coproporphyrin type III. The evidence today, however, is too fragmentary for this explanation to be accepted as more than a hypothesis.

Such a hypothesis, however, will not explain the production of porphyrin of type I in nearly all the cases studied. Porphyrins of types I and III cannot be converted the one into the other by chemical means without breakdown to simple pyrroles and resynthesis.⁴² It is extremely unlikely that the body can convert porphyrin of one type into that of another, and Fischer⁴² has emphasized the dual nature of the porphyrins in consequence. The studies of Dobriner^{35c} and of Watson^{35b} in particular have indicated further that coproporphyrin is chiefly if not entirely endogenous. The amounts excreted were greatest in cases of hemolytic jaundice and pernicious anemia or after hemorrhage or therapeutic hemolysis in a case of polycythaemia vera in which the regeneration and bone marrow activity were greatest, and they were least in a case of anemia associated with destruction of bone marrow.⁴³

38 Grotepass, W. Zur Kenntnis des im Harn auftretenden Porphyrins bei Bleivergiftung, *Ztschr f physiol Chem* **205** 193, 1932. Franke, K., and Litzner, G. Quantitative Determination of Porphyrin in Urine as an Aid in Early Recognition of Lead Poisoning, *Ztschr f klin Med* **129** 115, 1935. Roth, E. Lead Poisoning and Porphyria, *ibid* **129** 123, 1935. Watson,^{35b} 1936.

39 Dobriner, K., and Rhoads, C. P. The Excretion of Porphyrin in Refractory and Aplastic Anemia, *J Clin Investigation* **17** 125, 1938.

40 Watson, C. J. The Porphyrins and Their Relation to Disease. Porphyria, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, London, Oxford University Press, 1938, vol 4, pt 1, p 228 (1). Dobriner^{35c}.

41 van den Bergh, A. A. H., Grotepass, W., and Revers, F. E. Beitrag uber das Porphyrin in Blut und Galle, *Klin Wchnschr* **11** 1534, 1932.

42 Fischer, H. Ueber Porphyrine und ihre Synthesen, *Ber d deutsch chem Gesellsch* **2** 2611, 1927, Ueber Hamin und Porphyrine, *Verhandl d deutsch Gesellsch f inn Med* **45** 7, 1933. Fischer and Orth¹⁹.

43 Dobriner, K., Strain, W. H., and Localio, S. A. (a) I Quantitative Measurement of Coproporphyrin and Total Coproporphyrin I Excretion in Normals, *Proc Soc Exper Biol & Med* **36** 752, 1937, (b) II Coproporphyrin I Metabolism and Hematopoietic Activity, *ibid* **36** 755, 1937.

The studies of Dobriner and his collaborators⁴⁴ have further shown a parallelism between the rates of excretion of coproporphyrin type I and the rates of excretion of urobilinogen. These various investigations led Dobriner, Localio and Strain⁴⁵ to suggest that the synthesis of porphyrins in vivo is directed to the formation of large amounts of type III porphyrin and a small amount of type I porphyrin as products of the same synthesis. Physiologically there is a direct proportion between the construction of the two types of porphyrin. Type III porphyrin is used in the formation of the respiratory pigments, and type I porphyrin is excreted mainly as coproporphyrin I. Since an increase or decrease in the synthesis of hemoglobin is paralleled by the formation and excretion of type I porphyrin, the excretion of coproporphyrin I has been used by Dobriner, Strain and Localio⁴³ and by Dobriner and Rhoads^{44b} as an index of hematopoietic activity both in normal persons and in persons in whom there is an orderly increase or decrease in hematopoiesis. Borst and Konigsdorffer⁴⁶ and Turner⁴⁷ have pointed out that there is formation of uroporphyrin I associated with the fetal megaloblastic type of erythropoiesis. Protoporphyrin has been found in marrow erythroblasts⁴⁶ and in human reticulocytes⁴⁷. Watson^{35b} also found an increased excretion of protoporphyrin in the same instances in which the feces contained increased amounts of coproporphyrins. This protoporphyrin was not finally identified but showed differences in behavior which suggested that it was not the same as protoporphyrin type III derived from hemoglobin. This evidence is in accord with the studies of Dobriner and his co-workers in linking the production of coproporphyrin I with erythropoietic activity.

The results thus far have shown that the liver plays an important role in the excretion and possibly in the metabolism of the porphyrins. In most instances the excreted porphyrin is type I coproporphyrin⁴⁸. However, in some diseases type III coproporphyrin has been recovered⁴⁹.

44 (a) Dobriner, K. Excretion of Porphyrin by Dogs. *Proc Soc Exper Biol & Med* **36** 757, 1937. (b) Dobriner, K., and Rhoads, C. P. The Excretion of Coproporphyrin I Following Hemorrhage in Dogs, *J Clin Investigation* **17** 105, 1938, *Metabolism of Blood Pigments in Pernicious Anemia*, *ibid* **17** 95, 1938. (c) Dobriner, Strain and Localio⁴³.

45 Dobriner, K., Localio, S. A., and Strain, W. H. A Study of the Porphyrins Excreted in Congenital Porphyrinuria, *J Biol Chem* **114** 2261, 1936. van den Bergh, Grotepass and Revers⁴¹. Fischer⁴². Footnote 44.

46 Borst, M., and Konigsdorffer, H. Untersuchungen über Porphyrin, Leipzig, S. Hirzel, 1929.

47 Watson, C. J., and Clarke, W. The Occurrence of Protoporphyrin in the Reticulocytes, *Proc Soc Exper Biol & Med* **36** 65, 1937.

48 Watson^{35b}. Dobriner^{35c}.

49 Vigliani, E., and Angeleri, C. Ueber das im Plasma Bleikranker vorkommende Porphyrin, *Klin Wchnschr* **15** 700, 1936. Vigliani, E. and Waldenstrom, J. Die Porphyrine beim Saturnismus, *Deutsches Arch f klin Med* **180** 182, 1937. Dobriner^{35c}.

Garrod²⁷ and Gunther²⁸ in their early work noted an increased urinary excretion of porphyrin in cases of hepatic disease. Quantitative data on urinary porphyrin have been recorded by Thiel,⁵⁰ Boas⁵¹ and Lageder.⁵² Brugsch⁵³ measured the urinary output of coproporphyrin before and after a meal of liver and concluded that an increase in the urinary coproporphyrin content following such a meal is a sensitive indicator of hepatic insufficiency. Tropp and Penew⁵⁴ have recently published more complete data on the relation of the porphyrins to hepatic damage, as have also Kammerer and Meyer.⁵⁵ All these studies indicate that an increased urinary output of porphyrin is an early indication of hepatic insufficiency.

The observed increase in the urinary output of coproporphyrin is perhaps due to two factors—an increased production and an inability to excrete porphyrins into the bile on the part of the damaged liver. If so, there is a marked similarity between the pathway of excretion of the porphyrins and that of urobilinogen and bile pigments.

The entire subject is in its infancy. All authors, with the exception of Brugsch, have determined only the urinary output of coproporphyrin. The studies of fecal porphyrin conducted by Brugsch, however, were inconclusive, since the various porphyrins excreted were not separated. With the newer methods now available it appears that accurate determinations of the urinary and fecal output of coproporphyrin can be made. Studies utilizing these methods to determine the ratio between the urinary and the fecal output of coproporphyrin, as suggested by Brugsch, will yield valuable information. The studies thus far indicate that in hepatic disease there is a shift of the ratio between the urinary output and the fecal output of coproporphyrin in favor of the urinary porphyrins.

50 Thiel, W., and Kammerer, H. Quantitative Porphyrinmessungen bei verschiedenen Krankheiten, *Verhandl d deutsch Gesellsch f inn Med* **45** 81, 1933.

51 Boas, J. Ueber das Vorkommen von Protoporphyrin im Harn, *Klin Wchnschr* **12** 589, 1933.

52 Lageder, K. Klinische Porphyrinuntersuchungen mit einer quantitativen spektroskopischen Methode, *Arch f Verdauungskr* **56** 237, 1934.

53 Brugsch, J. T. Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen, *Ztschr f d ges exper Med* **95** 471, 482 and 493, 1935. Keys, A. and Brugsch, J. T. Porphyrins and Porphyrinemia, *Am J Digest Dis & Nutrition* **5** 49, 1938.

54 Tropp, C., and Penew, L. Quantitative Clinical Study of the Urinary Porphyrin in Hepatic Cirrhosis, Hepatopathies Exclusive of Cirrhosis. Tuberculosis and Other Diseases. Improved Technic of Determining the Porphyrins, *Deutsches Arch f klin Med* **180** 423, 1937.

55 Kammerer, H., and Meyer, W. K. Ueber abdominale idiopathische Porphyrrie, *Deutsches Arch f klin Med* **179** 392, 1936.

PHOSPHATASE IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

The various tests of hepatic function which have been recommended as of value in the differential diagnosis of jaundice are legion. The status of many of them has been discussed in previous articles of this series or in such articles as the recent one of Snell and Magath,⁵⁶ in which most of the generally accepted tests have been discussed. Much controversy has arisen over the diagnostic significance of the phosphatase values of the serum in jaundice.⁵⁷ Roberts⁵⁸ first reported that this value is increased in obstructive jaundice. He obtained normal values in cases of hepatitis or catarrhal jaundice and so suggested the use of this test in making a differential diagnosis. This view has been substantiated by the reports of Armstrong,^{58a} Rothman, Meranze and Meranze,⁵⁹ and Flood, Gutman and Gutman.⁶⁰ The elevation of the phosphatase content in cases of obstructive jaundice is accepted, as is the finding of normal values in cases of hemolytic jaundice. Such cases have been reported by Roberts,⁵⁸ Greene, Shattuck and Kaplowitz,⁶¹ Herbert,⁶² Anderson,⁶³ and Flood, Gutman and Gutman.⁶⁰

The majority of investigators who have studied the phosphatase content in cases of hepatitis or of catarrhal jaundice have reported variable results. Normal values frequently are obtained. Elevated values are met with sufficient frequency markedly to limit the diagnostic value of this test, if not to render it valueless.⁶⁴

56 Snell, A. M., and Magath, T. B. The Use and Interpretation of Tests for Liver Function. A Clinical Review, *J. A. M. A.* **110** 167 (Jan 15) 1938.

57 Cantarow, A. Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, *Internat. Clin.* **1** 230, 1936. Morris, N., and Peden, O. D. Plasma Phosphatase in Disease. A Review, *Quart. J. Med.* **6** 211, 1937.

58 Roberts, W. M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit. J. Exper. Path.* **11** 90, 1930. Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit. M. J.* **1** 734, 1933.

58a Armstrong, A. R., King, E. J., and Harris, R. I. Phosphatase in Obstructive Jaundice, *Canad. M. A. J.* **31** 14, 1934.

59 Rothman, M. M., Meranze, D. R., and Meranze, T. Blood Phosphatase as an Aid in Differential Diagnosis of Jaundice, *Am. J. M. Sc.* **192** 526, 1936.

60 Flood, C. A., Gutman, E. B., and Gutman, A. B. Phosphatase Activity, Inorganic Phosphorus and Calcium of Serum in Disease of the Liver and Biliary Tract. A Study of One Hundred and Twenty-Three Cases, *Arch. Int. Med.* **59** 981 (June) 1937.

61 Greene, C. H., Shattuck, H. F., and Kaplowitz, L. The Phosphatase Content of the Blood Serum in Jaundice, *J. Clin. Investigation* **13** 1079, 1934.

62 Herbert, F. K. The Plasma Phosphatase in the Various Types of Jaundice. *Brit. J. Exper. Path.* **16** 365, 1935.

63 Anderson, R. G. The Plasma Phosphatase in Jaundice, *St. Barth. Hosp. Rep.* **68** 221, 1935.

64 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. IV. Serum Phosphatase of Non-Osseous Origin, Significance of the Variations of Serum Phospha-

The results of experimental studies likewise have been variable. The phosphatase content is increased in experimental obstructive jaundice in dogs⁶⁵ but not in cats⁶⁶. Toxic injury to the liver in dogs by a variety of methods has been shown by Hartman and Schelling⁶⁷ and by Armstrong and King⁶⁸ to produce an increase. A similar increase has been observed in cases of complete biliary fistula. No satisfactory single explanation of these various and apparently contradictory clinical and experimental observations has been propounded thus far. Thannhauser and his collaborators⁶⁹ have reported recently an extensive series of observations which offer an alternative explanation and do much to clarify the situation.

Bodansky⁷⁰ observed that there was a paradoxical increase in the phosphatase content of serum on standing. Thannhauser found that cevitamic acid was an intense activator of serum phosphatase. Normal subjects responded with an increase of from 100 to 134 units. Patients with hepatic disease or experimental animals with high initial values did not show such rises after the addition of cevitamic acid. He con-

tase in Jaundice, *Proc Soc Exper Biol & Med* **31** 107, 1933. Austoni, B., and Caggi, G. La phosphatase du plasma dans differentes affections, *Presse med* **42** 1594, 1934. Fiessinger, N., and Boyer, F. La phosphatase plasmatique en pathologie hepatique, *Rev med-chir d mal du foie* **10** 137, 1935. Cantarow, A., and Nelson, J. Serum Phosphatase in Jaundice, *Arch Int Med* **59** 1045 (June) 1937. Greene, Shattuck and Kaplowitz⁶¹. Herbert⁶². Anderson⁶³.

65 (a) Bodansky, A., and Jaffe, H. L. Phosphatase Studies. VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, *Proc Soc Exper Biol & Med* **31** 1179, 1934. (b) Armstrong, A. R., King, E. J., and Harris, R. I. Phosphatase in Obstructive Jaundice, *Canad M A J* **31** 14, 1934.

66 Cantarow, A., Stewart, H. L., and McCool, S. G. Serum Phosphatase in Cats with Total Bile Stasis, *Proc Soc Exper Biol & Med* **35** 87, 1936.

67 Hartman, F. W., and Schelling, V. Serum Phosphatase in Experimental Insufficiency of the Liver, *Arch Path* **18** 594 (Oct.) 1934.

68 Armstrong, A. R., and King, E. J. Serum Phosphatase in Toxic and Hemolytic Jaundice, *Canad M A J* **32** 379, 1935.

69 Thannhauser, S. J., Reichel, M., and Grattan, J. F. Studies on Serum Phosphatase Activity. I. Ascorbic Acid Activation on Serum Phosphatase, *J Biol Chem* **121** 697, 1937. Thannhauser, S. J., Reichel, M., Grattan, J. F., and Maddock, S. J. II. The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, *ibid* **121** 709, 1937, III. The Effect of Complete Biliary Fistula on Phosphatase Activity in Serum and Bile, *ibid* **121** 715, 1937, IV. The Deactivating Effect of Thiol Compounds and Bile Acids on Serum Phosphatase in Vitro and in Vivo, *ibid* **121** 720, 1937, V. Studies Concerning Increased Serum Phosphatase Values in Disease, *ibid* **121** 727, 1937. Maddock, S., Thannhauser, S. F., Reichel, M., and Grattan, J. F. A New Conception of Serum Phosphatase. Review of Experimental Work, *New England J Med* **218** 166, 1938.

70 Bodansky, A. Paradoxical Increase of Phosphatase Activity in Preserved Serum, *Proc Soc Exper Biol & Med* **29** 1292, 1932.

cluded that the high values previously reported are to be explained as due to an increased activation of phosphatase and not to an increase in the total amount of enzyme present in the serum. The exact nature of this activating factor is unknown. Bile acids which may be present in the serum, especially in cases of obstructive jaundice, decrease the activation of the phosphatase.

Thannhauser and his associates therefore pointed out that the mechanism producing an apparent increase in the serum phosphatase content in jaundice seemed to be understandable in the light of these findings. Any obstruction to the excretion of bile results in the damming up of both depressing (bile acids) and activating (cofactor) substances. Since the cofactor substances are more powerful as activators than are bile acids as depressors, the net result is an increase in activity of serum phosphatase. The difficulty of attempting to use phosphatase determinations in the differential diagnosis of hepatic disease is thus apparent.

PORTAL HYPERTENSION

The two cardinal symptoms of hepatic disease are jaundice and ascites. The first usually is considered indicative either of biliary obstruction or of acute toxic or infectious hepatitis. The second is accepted as pathognomonic of hepatic cirrhosis.

The ascites in cirrhosis usually is accompanied by opisthia (delayed excretion of urine), splenomegaly, hemorrhoids, gastrointestinal hemorrhages and the development of a collateral venous circulation over the abdomen. The clinical syndrome characterized by this set of signs and symptoms is observed in cases of hepatic cirrhosis but is not limited to such cases, for it may be seen in a miscellaneous group of other pathologic conditions. It is apparent that the common denominator responsible for the production of this clinical picture is that of engorgement of the portal circulation, with increased pressure in the portal vein. This syndrome, in consequence, has been called the syndrome of portal hypertension.

Though this syndrome is not discussed as such in many English and American textbooks, its recognition is not recent, for Stahl,⁷¹ in 1698, described some of its cardinal features. There were many others who contributed to the study of the condition, but it remained for Gilbert,⁷² in 1899, to crystallize clinical thought and to name the syndrome. The study of this condition has been furthered by the students

71 Stahl, G. E. *De vena portae, porta malorum hypochondriaco-splenetico-suffocativo-hysterico-cólico-haemorrhoidariorum*, Halle, 1698.

72 Gilbert, A., and Garnier, M. *De l'abaissement de la pression artérielle dans les cirrhoses alcooliques du foie*, Presse med 1 57, 1899.

of Gilbert and was discussed in detail in the monograph of Villaret and Justin-Besançon⁷³

The anatomy and physiology of the circulation of the liver and the changes which contribute to the development of vascular obstruction and portal hypertension in cases of portal cirrhosis have recently been summarized by McMichael,⁷⁴ McNee⁷⁵ and Weiss⁷⁶. A consideration of the relations within the vascular bed of the liver was initiated by Gad,⁷⁷ in 1873. He maintained that the finer branches of the hepatic artery and of the portal vein met at an acute angle so that wedge-shaped flap valves were formed by this angle of union. This flap then shifted in accordance with the pressure on each side so that an increased flow of blood through the hepatic artery would limit the flow through the portal vein. McMichael⁷⁴ objected to this view as not being in keeping with the bulk of anatomic evidence. Herrick,⁷⁸ in 1907, perfused human livers, both normal and cirrhotic, with saline solution. He concluded that the increased portal pressure in hypertrophic portal cirrhosis is due not to vascular obstruction from fibrosis but to the combined effect of the direct communication of the arterial pressure to the portal vein through dilated capillaries and to the larger volume of flow through the hepatic artery proportional to the portal flow in the cirrhotic as compared with that in the normal liver. McIndoe⁷⁹ on the other hand, reported that in cases of advanced hepatic cirrhosis the architecture of the liver is so disorganized that the parenchymal cells are almost completely divorced from the normal portal blood supply and are largely dependent on the hepatic artery for the maintenance of an adequate circulation. These changes he claimed were sufficient to explain the portal hypertension.

The studies of McIndoe were most convincing but did not tell the whole story. Bollman⁸⁰ has shown in dogs with damaged livers that

73 Villaret, M., and Justin-Besançon, L. Le syndrome d'hypertension portale, in Roger, G. H., Widal, F., and Teissier, P. J. *Nouveau traite de medecine*, Paris, Masson & Cie, 1928, vol. 16, p. 97.

74 McMichael, J. The Portal Circulation, *J. Physiol.* **75** 241, 1932.

75 McNee, J. W. Liver and Spleen. Their Clinical and Pathological Associations, *Brit. M. J.* **1** 1017 (June 4), 1068 (June 11) 1932.

76 Weiss, S. Portal Hypertension, *Internat. Clin.* **1** 149, 1932.

77 Gad, J. Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie, Inaug. dissert., Berlin, Gustave Schade, 1873.

78 Herrick, F. C. An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, *J. Exper. Med.* **9** 93, 1907.

79 McIndoe, A. H. Vascular Lesions of Portal Cirrhosis, *Arch. Path.* **5** 23 (Jan.) 1928.

80 Bollman, J. L. The Influence of Diet on the Production of Ascites, *Arch. Path.* **6** 162 (July) 1928. Snell, A. M., Greene, C. H., and Rowntree, L. G. Diseases of the Liver. VII. Further Studies in Experimental Obstructive Jaundice, *Arch. Int. Med.* **40** 471 (Oct.) 1927.

ascites may be produced or may be made to disappear at will by changes in the diet. Equally dramatic changes are seen in some patients as a result of the successful therapeutic use of mercurial diuretics. These changes are too rapid to be explained by the assumption that the ascites in portal cirrhosis is solely the result of portal obstruction from the fibrotic changes in the liver. Evidently other factors besides the degree of fibrosis affect the development of ascites. It is doubtful, however, if these accessory factors, which will be discussed later, can cause the development of ascites without the concomitant presence of portal obstruction.

Other conditions which may present the clinical syndrome of chronic portal obstruction with portal hypertension include thrombosis or phlebitis of the portal vein. Weir and Beaver⁸¹ reviewed 127 cases, including 54 cases of simple thrombosis. In 7 cases in which there was cardiac disease the thrombosis was complete enough to cause death. Symptoms developed acutely, and in all cases there was infarction of the small intestine. Infarction of the liver, on the other hand, did not follow thrombosis of the portal vein but developed only after occlusion of the hepatic artery. In some cases Weir and Beaver noted the development of a collateral circulation around the portal obstruction. Because they found transitional stages they interpreted thickening of the wall of the portal vein as part of the thrombotic process rather than as a primary degeneration of the wall of the vein.

Klemperer⁸² reviewed the literature on cavernomatous transformation of the portal vein and reported an additional case in which there were the symptoms of portal hypertension. He reported that these cases fell into three groups representing (1) the end result of portal thrombosis, (2) malformations and (3) tumor (angioma) of the vein. Simonds⁸³ has also reviewed the effects of chronic occlusion of the portal vein, and Wilson and Lederer⁸⁴ have described the microscopic anatomy and pathogenesis of portal phlebosclerosis.

The most interesting group of cases in which there is the syndrome of portal hypertension is that ill defined group characterized by splenomegaly, anemia, leukopenia and frequently cirrhosis of the liver,

81 Weir, J. F., and Beaver, D. C. Diseases of the Portal Vein. A Review of One Hundred and Twenty-Seven Instances, *Am J Digest Dis & Nutrition* **1** 498, 1934.

82 Klemperer, P. Cavernomatous Transformation of the Portal Vein. Its Relation to Banti's Disease, *Arch Path* **6** 353 (Sept.) 1928.

83 Simonds, J. P. Chronic Occlusion of the Portal Vein, *Arch Surg* **33** 397 (Sept.) 1936.

84 Wilson, S. J., and Lederer, M. Splenomegaly. Portal Phlebosclerosis, *Am J Dis Child* **38** 1231 (Dec.) 1929.

as well as by changes in the portal circulation. The syndrome in this group of cases does not correspond accurately to the syndrome described by Banti, yet for want of a better term it is often discussed under the title of Banti's syndrome. According to some observers, cases of portal (Laennec's, atrophic, alcoholic) cirrhosis properly belong in this group, apparent differences being due to variations in the order and time relations in the development of the disease. In many cases of so-called Banti's disease an etiologic factor, such as portal thrombosis, syphilis, adhesions or splenic ptosis, can be demonstrated, but in others the cause escapes detection.

There have been many theories to explain the origin of splenomegaly in the Banti syndrome. Toxic, inflammatory and compensatory factors have all been suggested as causal. More attention has been paid recently to the theory that the splenic changes, in part at least, are congestive and associated with portal hypertension. This theory has been stressed because of (1) the similarity of the clinical course in all cases in this group regardless of the primary cause, (2) the similarity of the pathologic changes, (3) the similarity of the response to splenectomy when performed in comparable stages of the disease and (4) the evidence for the existence of portal hypertension in all

CONGESTIVE SPLENOMEGALY

Many observers have emphasized the clinical similarity of the cases in this group. Eppinger stressed the congestive changes in the spleen. Larrabee⁸⁵ reviewed 47 cases which fell into this group and in all of which similar clinical features were present independent of the underlying etiologic process. He advocated early splenectomy in consequence. Engelbreth-Holm⁸⁶ presented several cases of tuberculous splenomegaly which clinically resembled cases of Banti's disease. In 2 of these the condition was relieved symptomatically after splenectomy. The pathologic changes in the spleen in cases of the Banti syndrome show a striking uniformity. This was stressed by Malloy,⁸⁷ who concluded that the histologic changes in the spleen could be accounted for by long-continued passive congestion. He pointed out the frequency with which an old thrombosis of the splenic vein may be overlooked and described a case in which an old recanalized throm-

85 Larrabee, R. C. Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, *Am J M Sc* **188** 745, 1934.

86 Engelbreth-Holm, J. A Study of Tuberculous Splenomegaly and Splenogenic Controlling of the Cell Emission from the Bone Marrow, *Am J M Sc* **195** 32, 1938.

87 Splenic Anemia, Cabot Case 20521, *New England J Med* **211** 1215, 1934.

bosis was recognized only by careful study of a series of microscopic sections Eppinger likewise discussed the influence of venous stasis and the *Stauungsmilz* at length Rousselot⁸⁸ reported that the characteristic microscopic changes in the spleen were scarring and the obliteration of the usual architecture The cellular elements in both red and white pulp were decreased The fibrosis included capsular and trabecular thickening together with interstitial fibrosis and so-called fibroadema of Banti There was a diminution in the number and in the size of the malpighian corpuscles

Rousselot also emphasized the observation of dilatation and tortuosity of the veins in the splenic pedicle, the veins sometimes dilating to two to four times the normal diameter Such changes were present in nearly all the cases reported by Rousselot, though in only half of them was there evidence of obstruction at the time of operation

McMichael⁸⁹ postulated the identity of the siderotic nodule, the periarterial fibrosis and the Banti fibroadema in the spleen He concluded that the vascular changes in the spleen and the concomitant endophlebitis were due in part to an increase in the portal pressure He also reported that microscopic or clinical evidences of hepatitis could be demonstrated in many cases in which there was no obvious cirrhosis His experimental studies on cats⁷⁴ showed that the injection of epinephrine produced vasoconstriction of the intrahepatic branches of the portal vein, with a consequent rise in the portal pressure Such observations are important, for some such mechanism acting in response to humoral or nervous stimulation may be responsible for increases in portal pressure in the absence of anatomically demonstrable obstruction

The similarity of the pathologic changes in the spleen in cases of Banti's syndrome with those produced by experimentally induced venous congestion in animals as reported by McMichael⁷⁴ and Jager⁹⁰ affords indirect evidence for the existence of portal congestion in these cases Numerous investigators, including Carnot, Gayet and Merklen,⁹¹ have measured the venous pressure in the portal vein in experimental animals

88 Rousselot, L M The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome, *J A M A* **107** 1788 (Nov 28) 1936

89 McMichael, J The Pathology of Hepato-Lineal Fibrosis, *J Path & Bact* **39** 481, 1934

90 Jager, E Ueber Stauungsmilz, *Verhandl d deutsch path Gesellsch* **26** 334, 1931

91 Carnot, P, Gayet, R, and Merklen, F P Exploration graphique des modifications de la pression veineuse porte liees a des excitations vaso-constrictives, *Compt rend Soc de biol* **104** 1260, 1930

Thompson and his associates⁹² have extended these studies to man. They determined the pressure in the splenic vein at operation by direct venipuncture after the operative delivery of the spleen and before ligation of any of the larger vessels. In 3 cases of typical hemolytic jaundice the pressure in the splenic vein did not rise above 125 mm of saline solution. In 8 cases in which there was the clinical syndrome of portal hypertension, the pressure in the splenic vein ranged from 250 to 500 mm of saline solution. The venous pressure in the antecubital veins, taken at the same time, ranged from 12 to 140 mm. Five of the cases of portal hypertension were due to the Laennec type of portal cirrhosis and 3 to cirrhosis from chronic schistosomiasis. It is to be hoped that studies such as these will be extended. They afford a direct measurement of the portal pressure in man which is obtainable in no other way. By demonstrating the presence of an increased pressure in the splenic vein in cases of the so-called syndrome of portal hypertension they have gone far in establishing the validity of a clinical picture which was established originally on a basis of logical deduction from indirect evidence.

The factor of venous stasis apparently does not explain the whole of the reaction of the spleen to venous congestion or the production of the associated clinical and hematologic pictures. Obstruction of short duration will not cause continued splenic enlargement, and Warthin⁹³ was unable to produce permanent splenomegaly by ligation of the splenic vein. The spleen may be enlarged in cases of cardiac failure but rarely to such degree that it is palpable below the costal margin. Possibly this is due to the relative short duration of the cardiac type of chronic passive congestion, for Larrabee considered five to six years the minimum time necessary for the production of the typical syndrome. Wohlwill⁹⁴ emphasized the fact that definite splenic thrombosis is not always accompanied by splenomegaly.

Jäger⁹⁵ remarked that recent work on the "reservoir function" of the spleen has shown great variation in different animal species as to the ratio between the capacity of the distended spleen and that of the contracted organ. It is therefore impossible to apply the experimental figures obtained for lower animals directly to man. An approximate

92 Thompson, W. P., Caughey, J. L., Whipple, A. O., and Rousselot, L. M. Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), *J. Clin. Investigation* **16** 571, 1937.

93 Warthin, A. S. The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease. *Internat. Clin.* **4** 189, 1910.

94 Wohlwill, F. Ueber Pfortadersklerose und Bantiähnliche Erkrankungen, *Virchows Arch. f. path. Anat.* **254** 243, 1925.

95 Jäger, E. Milzbau und Kreislaufstörung, *Virchows Arch. f. path. Anat.* **299** 531, 1937.

estimate of the effect of acute venous congestion on the human spleen may be obtained by distending the normal organ with saline solution. The distended spleen may triple its original weight, and it is unlikely that chronic venous congestion produces a greater degree of enlargement. On this assumption an average normal adult spleen weighing 150 Gm could enlarge to 450 Gm in response to chronic congestion. The finding of additional proliferative changes in larger spleens than this led Jager to suggest that while congestion alone would not produce marked splenomegaly (over 400 Gm) in an adult, it might initiate a series of additional pathologic changes to account for further increase in the size of that organ. Johnston⁹⁶ added that the age of the patient often determines the degree of splenomegaly, for when an obstructive factor is present the splenomegaly is greater in the younger patients. It must also be remembered that the clinical degree of splenomegaly is variable. The spleen will cease to be palpable during or immediately after a gastric hemorrhage, only to enlarge again after its cessation or after a transfusion. This is a clinical observation of some importance.

BLOOD FLOW IN THE PORTAL VEIN

The anatomic arrangement of the vascular supply within the liver has been studied in detail since the observations of Glisson⁹⁷ and other early anatomists. The profuse nature of the vascular supply has best been shown by the studies of Copher and Dick,⁹⁸ who found that the volume of the portal blood flow in dogs corresponds to 60 cc of blood per minute per hundred grams of liver. Higgins, Mann and Priestley⁹⁹ said they considered this of fundamental importance, for they showed that while in normal animals hepatic tissue is regenerated rapidly after surgical excision, the presence of an Eck fistula prevents such regeneration. Furthermore, in fowls, in which there is free porto-caval communication, excision of part of the liver does not lead to rapid regeneration of the remaining portion. They concluded, therefore, that the necessity of providing a capillary bed adequate to take care of the large portal blood flow is one of the essential factors in producing regeneration of the liver in normal experimental animals.

96 Johnston, J. M. Relation of Changes in the Portal Circulation to Splenomegaly of Bant's Type, *Ann Int Med* **4** 772, 1931.

97 Glisson, F. *Anatomia hepatitis*, The Hague, Arnold Leers, 1681, pp 349-350, figs 1 and 2.

98 Copher, G. H., and Dick, B. M. "Streamline" Phenomena in the Portal Vein and the Selective Distribution of Portal Blood in the Liver, *Arch Surg* **17** 408 (Sept) 1928.

99 Higgins, G. M., Mann, F. C., and Priestley, J. T. Experimental Pathology of the Liver. X. Restoration of the Liver of the Domestic Fowl, *Arch Path* **14** 491 (Oct) 1932.

In man the blood flow through the portal vein has not been studied directly. Glenard,¹⁰⁰ in 1890, observed that certain diseases have predilections for one lobe of the liver or the other. Tumor metastases, for example, sometimes affect one lobe to the exclusion of the other. Glenard therefore postulated differences between the right and the left lobe of the liver.

Physiologic differences between the two lobes were demonstrated by Copher, Dick and Koechig,¹⁰¹ who showed that the right lobe of the liver produced a greater volume of bile per gram of hepatic tissue than did the left lobe but that the latter produced a more concentrated bile.

A partial anatomic explanation was afforded by McIndoe and Counsellor,¹⁰² who studied the vascular supply of the liver by means of corrosion methods. They found that the right and the left branches of the portal vein supply separate portions of hepatic tissue, with no intercommunication. The two portions are sharply divided by the embryologic boundary between the right and the left lobe, which lies along a line from the fossa of the gallbladder to the entrance of the hepatic veins into the vena cava.

That there might be a similar separation in the distribution of blood flowing into the portal vein from the different branches was first demonstrated by Sérégé,¹⁰³ in 1901. He injected india ink into the splenic vein of a dog and found that it was deposited only in the left lobe of the liver. Bartlett, Corper and Long¹⁰⁴ injected emulsified olive oil into the splenic vein and likewise found that it was deposited in that area. They suggested that this specific distribution might be due to "streamlining" of the blood from the different tributaries of the portal vein.

Copher and Dick studied this phenomenon by the injection of a solution of trypan blue, which provides immediate visualization of the stained area. They were able to demonstrate at least three separate currents in the portal vein, coming from the splenic and from the large and the small mesenteric veins, respectively. Blood from the spleen, stomach and colon was distributed to the left lobe of the liver. Blood

100 Glenard, F. Des resultats de l'exploration du foie chez les diabetiques, *Lyon med* **44** 5, 1890.

101 Copher, G. H., Dick, B., and Koechig, I. Differences in Bile from the Two Sides of the Liver, *Am J Physiol* **87** 510, 1928.

102 McIndoe, A. H., and Counsellor, V. S. Bilaterality of the Liver, *Arch Surg* **15** 589 (Oct.) 1927.

103 Sérégé, H. Contribution à l'étude de la circulation du sang porte dans le foie et des localisations lobaires hépatiques, *J de méd de Bordeaux* **31** 271, 1901.

104 Bartlett, F. K., Corper, H. J., and Long, E. R. The Independence of the Lobes of the Liver, *Am J Physiol* **35** 36, 1914.

from veins draining the duodenum, pancreas and jejunum, thus including those sections of the intestinal canal primarily concerned in the digestion and absorption of foodstuffs, drained only into the right lobe of the liver

The question of "streamlining" in the venous system has been studied even more extensively by Franklin and McLachlin,¹⁰⁵ who have demonstrated this phenomenon in other veins beside the portal

The technic of roentgen cinematographic methods applicable to the study of the circulation was developed by Naegeli and Janker,¹⁰⁶ and the methods have been described by Janker¹⁰⁷ Franklin and Janker¹⁰⁸ applied these methods to the study of blood flow in the portal and hepatic veins of animals. They found that during inspiration the blood flow from the liver into the hepatic veins is increased and that there is simultaneous blockage of the return along the vena cava, for the shadow cast by the intrahepatic portion of the inferior vena cava was narrowed during inspiration. This apparent narrowing indicated either actual compression of the vessel or else displacement of the caval flow by the influx of a streamlined flow from the hepatic veins

COLLATERAL CIRCULATION

Acute and complete occlusion of the portal vein is incompatible with life, whether observed in patients as a result of thrombosis or produced experimentally in animals, as reported by Boyce, Lampert and McFetridge¹⁰⁹. Partial occlusion is not. If the occlusion is produced so gradually as to permit the development of venous collaterals, it may become complete without a fatal termination

The course and the extent of the collateral circulation which develops in consequence of portal obstruction or hypertension are well known. The cutaneous vessels over the abdomen and back become distended and in extreme cases may go on to the formation of true caput medusae

105 Franklin, K. J., and McLachlin, A. D. Streamlines in the Abdominal Vena Cava, *J. Physiol.* **86** 386, 1936

106 Naegeli, T., and Janker, R. Experimentell-röntgenologische und röntgenkinematographische Kreislaufstudien, *Deutsche Ztschr. f. Chir.* **232** 560, 1931

107 Janker, R. Die Röntgenkinematographie, ein Forschungs- und Lehrmittel. *Deutsche Ztschr. f. Chir.* **240** 52, 1933

108 Franklin, K. J., and Janker, R. Effects of Respiration upon the Venae Cavae of Certain Mammals, as Studied by Means of X-Ray Cinematography, *J. Physiol.* **81** 434, 1934, Respiration and the Venae Cavae, *ibid.* **86** 264, 1936, The Effect of Respiration upon the Circulation Through the Liver, as Studied by Means of X-Ray Cinematography, *ibid.* **89** 160, 1937

109 Boyce, F. F., Lampert, R., and McFetridge, E. M. Occlusion of the Portal Vein. Experimental Study with Its Clinical Application, *J. Lab. & Clin. Med.* **20** 935, 1935

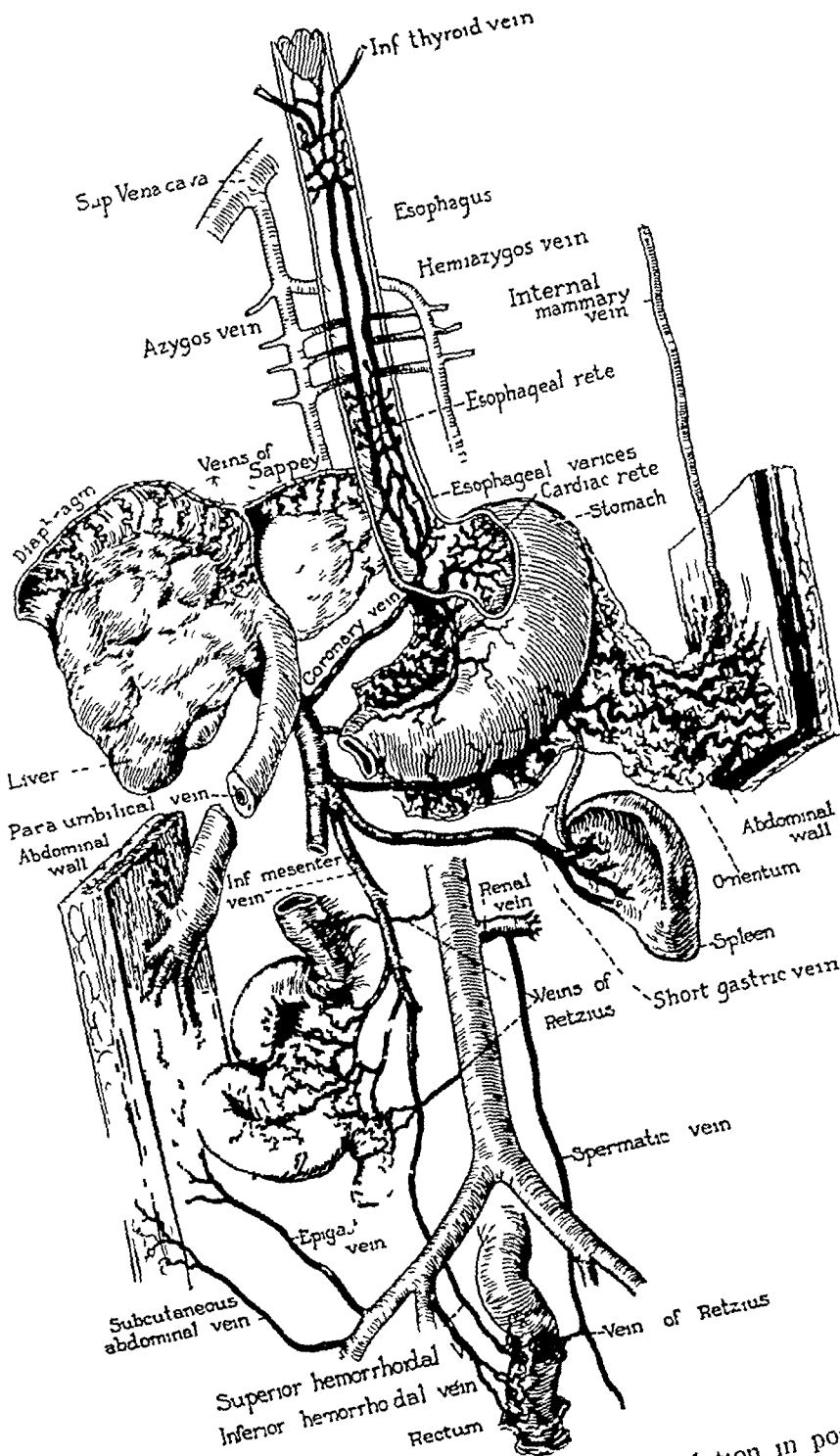


Fig 5—Diagram of the collateral venous circulation in portal cirrhosis, with especial reference to the anatomic features of the esophageal varices

The presence of venous distention in the latter condition is obvious, but the initial stages of the development of a collateral circulation often require careful examination for their recognition. In such cases the use of infra-red photography is a valuable clinical adjunct. This was introduced by Rawling,¹¹⁰ who pointed out that the maximal spectral transmission of light rays by the skin takes place in the infra-red zone. When venous congestion is present the veins are distended, and the contained blood is more venous in character. When photographed by the infra-red method, the veins therefore stand out more vividly than normal. Barker and Julin,¹¹¹ Payne,¹¹² Jones¹¹³ and others¹¹⁴ have



Fig 6—The collateral venous circulation over the abdomen in a case of portal cirrhosis with ascites. *A*, photographed by the ordinary method, *B*, photographed by the infra-red method (authors' case).

used this method for studying superficial venous distention, such as accompanies portal hypertension.

¹¹⁰ Rawling, S. O. *Infra-Red Photography*, London, Blackie & Son, Ltd 1933.

¹¹¹ Barker, N. W., and Julin, L. A. Demonstration of Superficial Veins by Infra-Red Photography, *Proc. Staff Meet., Mayo Clin.* **9** 58, 1934.

¹¹² Payne, R. T. *Infra-Red Photography of the Superficial Venous System*, *Lancet* **1** 235, 1934.

¹¹³ Jones, E. Demonstration of Collateral Venous Circulation in the Abdominal Wall by Means of Infra-Red Photography, *Am. J. M. Sc.* **190** 478, 1935.

¹¹⁴ Weisswange, W. M. H., and Friedrich, A. Versuche mit Infrarotaufnahmen in der Medizin, *Deutsche med. Wchnschr.* **62** 1540, 1936.

VENOUS BRUIT

When the collateral circulation is well developed a soft continuous bruit or hum may occasionally be heard over the abdomen, usually it is heard in the neighborhood of the xiphoid or of the umbilicus. First reported by Pegot,¹¹⁵ Bamberger¹¹⁶ and Trousseau¹¹⁷ it was later discussed in detail by Thayer¹¹⁸. Bates¹¹⁹ recently reported a case in which the bruit was heard at about the level at which the vena cava pierces the diaphragm. He, like Piazza-Martini,¹²⁰ concluded that this bruit was due to constriction of the inferior vena cava in its passage through the liver. Kenawy¹²¹ reported 6 additional cases of bilharzial cirrhosis in which a venous hum was present. In all the murmur was a localized continuous venous hum, frequently accompanied with a thrill. It was louder when the patient was sitting or standing than when he was recumbent. It was not associated with any primary cardiovascular abnormality. There was no relation between the intensity of the bruit and the presence of ascites or anemia. In one case the murmur disappeared after splenectomy. Kenawy concluded that this probably was due to the severance of some venous communication at the time of operation. In the majority of cases it seems as if the nature and the position of the hum were determined by the location and the character of the venous collaterals rather than by caval obstruction.

ESOPHAGEAL VARICES

The development of esophageal varices in cases of hepatic cirrhosis or of portal hypertension is well known, as is the danger of serious or fatal hematemesis from the rupture of such a varix. Plotz and Reich¹²² have considered this subject in some detail and have emphasized the importance of the early demonstration of such varices in the diagnosis of portal hypertension.

115 Pegot. Tumor variqueuse, avec anomalie du système veineux et persistance de la veine ombilicale, développement des veines sous-cutanées abdominales, *Bull Soc anat de Paris* **18** 49, 1833.

116 Bamberger, H. Granulierte Leber, *Wien med Wchnschr* **1** 5, 1851.

117 Trousseau, A. *Lectures on Clinical Medicine*, ed 3, translated by J. R. Cormack, London, New Sydenham Society, 1872, vol 5, p 131.

118 Thayer, W. S. On the Presence of a Venous Hum in the Epigastrium in Cirrhosis of the Liver, *Am J M Sc* **141** 313, 1911.

119 Bates, J. L. Continuous Venous Hum in Cirrhosis of the Liver, *Lancet* **1** 1108, 1937.

120 Piazza-Martini, V. Del rumore di soffio venoso udibile sull'area epatica, *Riforma med* **10** 663, 1894.

121 Kenawy, M. R. Continuous Venous Hum in Bilharzial Cirrhosis of the Liver, *Lancet* **1** 1281, 1937.

122 Plotz, M., and Reich, N. Esophageal Varices in Portal Hypertension. *Am J Digest Dis & Nutrition* to be published.

The anatomy and pathogenesis of esophageal varices have been studied carefully by Kegaries¹²³ The anastomosis on the portal side is composed of vessels from the coronary vein or veins and from the left gastroepiploic veins and the vasa brevia, which form a cardiac rete in the upper third of the stomach This second group of vessels is especially involved in some cases of splenic disease and may explain



Fig 7—Roentgenographic demonstration of the esophageal varices in a case of portal cirrhosis (authors' case)

the hemorrhage that occasionally follows ligation of the coronary vein or splenectomy At the cardia the veins are supported by a thick muscularis mucosae, and the mucosa is closely adherent to the sub-

123 Kegaries, D L Venous Plexus of the Esophagus, Surg, Gynec & Obst 58 46, 1934

mucosa In the lowest third of the esophagus the rich venous anastomosis of the submucosa is poorly supported by connective tissue and hence is a most favorable site for the formation of varicosities

The presence of esophageal varices may be inferred from hematemesis or may be demonstrated either by esophagoscopy¹²⁴ or roentgenographic methods



Fig 8—Roentgenographic demonstration of the esophageal varices in a case of portal cirrhosis (authors' case)

The latter method is increasing in favor and has been reported on by Schatzki,¹²⁵ Oppenheimer¹²⁶ and Brdiczka and Tschakert¹²⁷ Three

124 Moyer, S J Esophagoscopy Study of Esophageal Varices, *Arch Otolaryng* **10** 409 (Oct) 1929

125 Schatzki, R Relief Studies of the Normal and Abnormal Esophagus, Stockholm, P A Norstedt & Soner, 1936

126 Oppenheimer, A Esophageal Varices *Am J Roentgenol* **38** 403 1937

127 Brdiczka, I G, and Tschakert J The X-Ray Diagnosis of Esophageal Varices, *Fortschr a d Geb d Rontgenstrahlen* **46** 156 1932

stages have been recognized in the roentgenologic studies, although these sometimes merge into each other or may be seen on the same plate (1) the early stage, marked by a slight and diffuse venous congestion, resulting in moderate broadening of the rugae of the lower part of the esophagus, (2) beginning dilatation of larger individual veins which emerge from the submucosa and are marked by small rounded defects seen in the relief of the lowest portion of the esophagus, and (3) generalized enlargement of numerous veins which encroach on the mucosa. In the latter period the typical vermiform "negative shadows," or spaces, predominate. Successful visualization depends on several factors. The films should be exposed during forced inspiration, as the varices are distended at that time. They are seen most easily during the short interval between swallowing and complete emptying of the esophagus. The delay in the passage of the barium sulfate meal through the esophagus ranges from a second or two in early stages of congestion to several hours in the later stages, with superimposed cardiospasm. The esophageal stasis may be produced either by the mechanical obstruction of the varices or by the cardiospasm. The presence of food particles, polyps, a malignant growth, syphilis or cardiospasm must be excluded in making a differential diagnosis. All these can usually be excluded on roentgenographic evidence alone. The development of the roentgen diagnosis of esophageal varices is one of the most significant recent advances in the diagnosis of conditions associated with portal hypertension.

SURGICAL TREATMENT OF ASCITES AND HEMATEMESIS

There have been a multitude of attempts by surgeons to relieve the ascites and prevent hematemesis in cases of hepatic cirrhosis and portal hypertension. These have been reviewed by Zechel¹²⁸ in some detail. The main lines of surgical attack which have been suggested, either singly or in combination, are

- 1 To promote drainage of the ascitic fluid out of the abdominal cavity into the bladder, pleural cavity, lumbar musculature, subcutaneous tissues or lymphatic or venous system by a variety of mechanical devices

- 2 To establish a venous shunt around the liver by direct anastomosis between the portal vein and the inferior vena cava (Eck fistula) or then bianches

- 3 To further the development of a collateral circulation by visceropexy or omentopexy. This is one of the simplest operations from the standpoint of the surgical technic involved and thus far has been one of the most popular. In many cases the results are disappointing,

¹²⁸ Zechel, G. Cirrhosis of the Liver as a Surgical Problem, Illinois M J 70 560, 1936

but brilliant exceptions occur. Grinnell¹²⁹ reported that he had performed omentopexy in 23 cases of portal cirrhosis with satisfactory results in 10.

4 To decrease the portal blood supply by vascular ligation. Splenectomy is the most popular operation of this type and is replacing ligation of the splenic vessels, though Watson¹³⁰ has recommended the latter. The types of cases reported are so varied and the experience of any individual surgeon is so slight that it is difficult to evaluate this operation from a study of the literature. Pemberton¹³¹ reported that its value was established in the Banti syndrome, or splenic anemia. The results of splenectomy are less satisfactory when splenomegaly is complicated by well defined hepatic cirrhosis. Occasionally recovery is obtained in apparently hopeless cases, as in the one reported by Deaver and Reimann.¹³² Mandel and Marcus¹³³ said they were encouraged by the results of splenectomy as a means of preventing gastrointestinal hemorrhages in cases of portal cirrhosis. Mayo,¹³⁴ on the other hand, found that, in general, the results after splenectomy were no better than those after omentopexy. Walters, Rowntree and McIndoe¹³⁵ tried to reduce the local blood flow and pressure in the esophageal plexus and so prevent the rupture of esophageal varices and resultant hematemesis by ligation of the coronary vein of the stomach. In a few cases the results were satisfactory, but the reported series was small. Venous connections between the spleen and the greater curvature of the stomach or large veins extending from the spleen along the under surface of the diaphragm may serve to provide an oversupply of blood to esophageal varices and produce recurrent hemorrhage after ligation of the coronary vein. It seems probable that if this operation is to be successful it must be combined with splenectomy, at least in certain cases.

5 To diminish transudation from the portal system into the peritoneal cavity and obliterate part of the portal bed by resection of a portion

129 Grinnell, R. S. Omentopexy in Portal Cirrhosis of the Liver with Ascites. A Review of Twenty-Three Cases, *Ann Surg* **101** 891, 1935.

130 Watson, R. B. Ligation of Splenic Artery for Advanced Splenic Anemia, *Brit M J* **1** 821, 1935.

131 Pemberton, J. deJ. Results of Splenectomy in Splenic Anaemia, Haemolytic Jaundice, and Haemorrhagic Purpura, *Ann Surg* **94** 755, 1931.

132 Deaver, J. B., and Reimann, S. P. Splenic Enlargement with Cirrhosis of the Liver, *Ann Surg* **88** 355, 1928.

133 Mandel, E., and Marcus, G. Zur Behandlung von Varicenblutungen bei Lebercirrhose durch Splenektomie, *Ztschr f klin Med* **128** 504, 1935.

134 Mayo, W. J. Review of Five Hundred Splenectomies, *Ann Surg* **88** 409, 1928.

135 Walters, W., Rowntree, L. G., and McIndoe, A. H. Ligation of Coronary Veins for Bleeding Esophageal Varices, *Proc Staff Meet, Mayo Clin* **4** 146, 1929.

of the intestine Fuller and her associates¹³⁶ reported a case in which the operation was successfully performed and the patient was free from ascites twenty-nine months after the resection of slightly less than 7 feet (213 cm) of small intestine. This is a most radical procedure, and the reader is referred to their article for the arguments whereby they seek to justify its use.

One of the reasons why splenectomy has not been more popular in the treatment of portal hypertension and ascites has been the danger of postoperative thrombosis. Rosenthal¹³⁷ found great differences in the numbers of blood platelets and concluded that splenomegaly in part may represent an attempt to regulate the distribution of platelets. He further divided his cases with regard to thrombopenia and thrombocythemia. The prognosis was better in association with the former, and postoperative thrombosis was frequent in association with the latter. Evans¹³⁸ reported confirmatory results, while Graham Bryce¹³⁹ and Rousselot⁸⁸ did not find a correlation between the initial platelet count and the postoperative course. Moore¹⁴⁰, Englebreth-Holm, and Smith and Farber¹⁴¹ likewise reported cases which seemed to refute Rosenthal's hypothesis. Further study along this line, with a search for better preoperative prognostic criteria, is urgently indicated.

Another possible solution of the problem of postoperative thrombosis has been suggested by the work of Best and his colleagues,¹⁴² who have prepared heparin with a purity suitable for intravenous use in quantity. The use of such a preparation to render the blood incoagulable or slowly coagulable, as suggested by Hedenius and Wilander,¹⁴³ promises to be of value in preventing thrombosis not only after splenectomy but after a wide range of surgical procedures.

136 Fuller, M. K., Cook, D. D. M., Walter, O. M., and Zbitnoff, N. Enterectomy in the Surgical Treatment of Hepatic Cirrhosis or Portal Obstruction with Ascites, *Surg., Gynec. & Obst.* **65** 331, 1937.

137 Rosenthal, N. Clinical and Hematologic Studies on Banti's Disease. Blood Platelet Factor with Reference to Splenectomy, *J. A. M. A.* **84** 1887 (June 20) 1925.

138 Evans, W. H. The Blood Platelets in Splenic Anemia, *Lancet* **1** 277, 1929.

139 Graham Bryce, A. Splenectomy and Thrombosis, *Lancet* **2** 1423, 1932.

140 Moore, S. W. Portal Thrombosis Following Splenectomy for Splenic Anemia, *Surg., Gynec. & Obst.* **63** 382, 1936.

141 Smith, R. M., and Farber, S. Splenomegaly in Children with Early Hematemesis, *J. Pediat.* **7** 585, 1935.

142 Murray, W. G., Jaques, L. B., Perrett, T. S., and Best, C. H. Heparin and Thrombosis of Veins Following Injury, *Surgery* **2** 163, 1937.

143 Hedenius, P., and Wilander, O. The Influence of Intravenous Injections of Heparin in Man on the Time of Coagulation. *Acta med. Scandinav.* **88** 443 1936.

ACCESSORY FACTORS IN THE PRODUCTION OF ASCITES

While the presence of mechanical obstruction to the passage of portal blood through the cirrhotic liver, with resultant portal hypertension, is universally accepted as a factor, it is doubtful if it alone is sufficient to account for the production of ascites. We have previously stressed the importance of accessory factors in the production of ascites, but the assignment of the role played by each is difficult. Chronic obstruction of the portal vein will not produce permanent ascites. It is likely that sufficient additional obstruction to produce temporary ascites results when the partial obstruction of cirrhosis is augmented by passive congestion, vasomotor disturbances, cloudy swelling of the hepatic parenchyma, serous hepatitis or thrombosis of the portal radicles in the liver. Chronic perihepatitis or peritonitis is a frequent concomitant of cirrhosis and may be responsible for some of the ascites. Toxic factors have been described as responsible for the development of ascites. These as yet undefined toxins may act either by increasing the degree of portal obstruction or by changing the capillary permeability of the portal area, thus allowing the transudation of a greater amount of fluid or interfering with its resorption.

The effect of changes in the serum protein is better understood. This subject was reviewed a year ago by Greene, Handelsman and Babey. They referred to the accumulated literature indicating that in hepatic disease and especially in cirrhosis there is a reduction in the serum protein content. The frequency with which the Takata-Ara¹⁴⁴ and similar tests give positive results indicates that there is a concomitant change in the serum proteins. This is also shown by the change in the viscosity of the blood serum reported by Kaunitz and Kent¹⁴⁵. Furthermore, the experiments of Butt and Keys¹⁴⁶ and of Snell¹⁴⁷ showed that not only is the serum protein value decreased in cases of cirrhosis but there is a disproportionate reduction in the colloidal osmotic pressure. This change is in a direction which directly favors the production of ascites. Further evidence of the change in

144 Ucko H. Serum Test for Diagnosis of Liver Disturbances, *Guy's Hosp Rep* **86** 166, 1936. Magath, T. C. The Takata-Ara Test of Liver Function *Am J Digest Dis & Nutrition* **2** 713, 1936. Boccia D., and Gamalero, J. A. Takata-Ara Reaction in Internal Diseases, *Semana med* **2** 365, 1936.

145 Kaunitz, H., and Kent, H. Relative Viscosity of Blood Serum in Persons With and Without Hepatic Disorders and Its Relation to Protein Content and Its Fractions, *Ztschr f klin Med* **132** 670, 1937.

146 Butt H. R., and Keys, A. Colloid Osmotic Pressure. Studies of Normal Individuals and of Those with Hypoproteinemia, *Proc Staff Meet, Mayo Clin* **12** 566, 1937.

147 Snell, A. M. The Value to Clinical Medicine of Experimental Studies on the Liver, *Ann Int Med* **11** 581 1937.

the protein value has been furnished by Kendall¹⁴⁸ He has analyzed human serum by means of specific antiserums and has found that the globulin fraction can be separated into at least two fractions which have distinct antigenic properties Normal serum contains between 1.1 and 2.1 per cent of alpha globulin and between 0.4 and 1 per cent of globulin x In patients with cirrhosis both the quantities and the proportions of these two are markedly changed from the normal It is to be hoped that further work along these lines may clarify the role of changes in the serum protein values in the development of ascites

148 Kendall, F. E. Studies on Serum Proteins. I. Identification of a Single Serum Globulin by Immunological Means, Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, *J. Clin. Investigation* **16** 921, 1937

News and Comment

Congress of American Physicians and Surgeons—The sixteenth session of the Congress of American Physicians and Surgeons will be held in Atlantic City, N J, May 3 and 4, 1938. The congress is made up of the following constituent societies and of guests specially invited by the executive committee: the American Otological Society, American Neurological Association, American Gynecological Society, American Laryngological Association, American Surgical Association, American Clinical and Climatological Association, Association of American Physicians, American Association of Genito-Urinary Surgeons, American Orthopedic Association, American Pediatric Society, American Association of Pathologists and Bacteriologists and American Dermatological Association.

All physicians are invited to attend the meetings of the congress and the public meetings of the societies, but only physicians who are members, specially invited guests or visitors accredited through members of the Constituent societies may register. The registration office will be in the parlor of Haddon Hall (headquarters hotel). Members and accredited visitors will be asked to pay a registration fee of \$5, invited guests will register but will not pay the registration fee. A copy of the published transactions of the congress will be sent to all members, invited guests and accredited visitors who register. The president of the congress, Dr James B Herrick, will deliver an address on Tuesday evening, May 3, in the Vernon Room of the headquarters hotel, and ladies, guests and visitors are invited to attend. A reception for the president will be held immediately thereafter. Further information may be procured from the chairman of the committee of arrangements, Dr J Torrance Rugh, 912 Medical Arts Building, Philadelphia.

American Association for the Study of Goiter—It is announced that the Third International Goiter Conference is to convene in Washington, D C, Sept 12 to 14, 1938. The official language of the conference will be English. Interpreters will be furnished for authors reading papers in other languages.

Any one desiring to participate in the program is requested to submit the title of his paper at his earliest convenience. All papers and discussions presented at the meetings are to be published in extenso in the form of transactions.

Further information concerning the conference can be secured by communicating with the officers of the American Association for the Study of Goiter or with the chairman of the program committee, Dr Allen Graham, 2020 East Ninety-Third Street, Cleveland.

American Heart Association—The fourteenth scientific session of the American Heart Association will be held on June 10 and 11, 1938, from 9 30 a m to 5 30 p m, in the Sir Francis Drake Hotel, San Francisco. On Friday, June 10, the general program on the heart will be given, and on Saturday, June 11, the program of the Section for the Study of the Peripheral Circulation will be presented.

Gesellschaft für Verdauungs- und Stoffwechselkrankheiten—The fourteenth meeting of the Society for Digestive and Nutritional Diseases will take place Sept 22 to 24, 1938, in Stuttgart under the presidency of Prof Grafe, of Würzburg, in connection with the meeting of scientists. The preliminary program is to include works on lipoidosis, glycogen storage disease, modern insulin treatment, pancreatitis and gastrointestinal autointoxication.

Book Reviews

Radiation Therapy Its Use in the Treatment of Benign and Malignant Conditions By Ira I Kaplan, B S, M D Price, \$10 Pp 558, with 198 illustrations New York Oxford University Press, 1937

This book is based on the author's experience in the use of radiation therapy in the treatment of benign and malignant diseases and on his wide knowledge of the literature as editor of the therapeutic section of the "Year Book of Radiology." While considerable detail has necessarily been omitted, a comprehensive and practical survey of the fields of radium, roentgen and electrosurgical therapy in the treatment of various pathologic conditions is included in this work.

The first five chapters deal with the historical development, physics, dosages and general considerations of radiation therapy. The next fifteen chapters are concerned with the pathologic conditions of the various special systems in which radiation therapy is employed. Chapter 21 is devoted to the complications and injuries following irradiation and contains timely warnings of value to all who use the various agents. A short discussion of the relation of trauma to cancer is included in the next chapter. The author's chapter on the nursing care of the patient with a malignant condition deals with the preparation and care of the patient before, during and after irradiation. He stresses the importance of the psychologic approach of the nurse toward the patient. The final chapter includes recommendations regarding the equipment needed for a department of radiation therapy.

In the discussion of each pathologic condition, brief descriptions of the clinical and of the pathologic picture of the lesion are included. The relation of special pathologic features and lymphatic drainage in malignant conditions to the form of therapy recommended is also considered. The various forms of therapy available and the indications for each type are discussed. Of special value is the consideration of the relation and importance of coordination of surgical, electrosurgical, roentgen and radium therapy. The discussions of the various technics are clear and may be duplicated by the experienced radiologist.

This book is well illustrated, readable, concise and practical. A short bibliography is included at the end of each chapter, and this feature should prove valuable for reference purposes.

Die experimentellen Grundlagen der Erkennung und Behandlung der allergischen Krankheiten By Paul Kallos and Liselotte Kallos-Deffner Pp 307, with illustrations Berlin Julius Springer, 1937

These writers review the literature on the theory of allergy and describe some experiments of their own on the production of bronchial asthma in guinea pigs. They argue that allergy is simply a special type of antigen-antibody reaction of a predominantly local nature. They are satisfied that the product of this reaction which causes the symptoms is a histamine-like compound. For therapy, the usual measures—specific desensitization, calcium preparations, atropine preparations and epinephrine-like substances—are deemed to be rational. The monograph is more a review than a presentation of novel ideas.

ARACHNODACTYLY AND ITS MEDICAL COMPLICATIONS

PALMER HOWARD FUTCHER, MD

AND

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BALTIMORE

Although there are at present in the neighborhood of two hundred reported cases of arachnodactyly, the syndrome is little known to the members of the American medical profession. Most of the literature is in French or German, and in this country few but ophthalmologists are familiar with the condition. Since arachnodactyly should interest orthopedists, pediatricians and physicians in general, as well as ophthalmologists, we wish to summarize its characteristics and report two cases with particular reference to the medical complications.

Described first, in 1896, by Marfan¹ as "pattes d'araignée" or "dolichosténomélie," the condition acquired the more familiar name arachnodactyly (spider fingers) from Achard² in 1902. The first case recognized in America was described by Piper and Irvine-Jones,³ in 1926. Comprehensive articles on arachnodactyly have been published by Young,⁴ Ormond,⁵ Weve,⁶ and Burch.⁷ The syndrome is familial and congenital, with the following major characteristics:

- 1 Abnormally long gracile fingers and toes
- 2 A decrease in the usual amount of subcutaneous fat
- 3 Generalized underdevelopment of the musculature
- 4 Relaxation of the ligaments

From the Department of Medicine, Johns Hopkins Hospital

1 Marfan, A. B. Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull et mém Soc med d hôp de Paris **13** 220-226 (Feb 28) 1896

2 Achard, C. Arachnodactylie, Bull et mem Soc méd d hôp de Paris **19** 834-840 (Oct 10) 1902

3 Piper, R. K., and Irvine-Jones, E. Arachnodactylia and Its Association with Congenital Heart Disease, Am J Dis Child **31** 832-839 (June) 1926

4 Young, M. L. Arachnodactyly, Arch Dis Childhood **4** 190-214 (Aug) 1929

(Footnotes continued on next page)

In addition each of the following characteristics is found in 50 per cent or more of the cases

5 Bilateral dislocation of the lens, with a tremulous condition of the iris (iridodonesis) and contracture of the pupil (not dilating normally under the influence of atropine sulfate)

6 Congenital abnormalities of the structure of the heart

7 Prominent ears

8 A highly arched palate

9 A tendency to infantilism

10 Kyphosis, scoliosis, deformities of the sternum and asymmetry of the thorax

11 Deformities of the joints, especially of the feet, with associated contractures

Marfan's syndrome is commonly noted in children. The diagnosis is made almost at a glance. The patient is usually tall and at the same time underweight for his age. The extremities are increased in length disproportionately to the stature. As Young⁴ has demonstrated, this is due to a marked increase in length of the metacarpals, metatarsals and phalanges, without a proportional increase in the diameter of these bones. Thus the hands and feet are abnormally long and narrow. Often the fingers are slightly webbed. At the same time the musculature of the arms and legs is markedly underdeveloped, and there is practically no subcutaneous fatty tissue. As a result, all bony prominences are marked, and emaciation accentuates the length of the extremities and enhances the slender spidery appearance of the arms and legs. To complete the picture, there is marked hypermotility of the joints of the extremities, owing to the relaxation of the ligaments, the patella can be partially dislocated at will, and often the fingers can be contorted into grotesque positions. There is no evidence of amyotonia, and the efficiency of the muscles is normal. Frequently there are secondary contractures. Full extension of the fingers is sometimes impossible. Flat foot, hammer toe and clubbing of the foot, similar to that seen in Friedreich's ataxia, are all common. Roentgenograms of the skeletal system reveal long, narrow bones, with no evidence of periosteal bone formation commensurate with the increased epiphyseal activity, a finding contrary to that in acromegaly. Some authors describe evidence of actual decalcification, but the few studies in which the calcium and phosphorus metabolism has been reported have

5 Ormond, A. W. The Etiology of Arachnodactyly, with Special Reference to Ocular Symptoms, *Guy's Hosp Rep* **80** 68-81 (Jan) 1930

6 Weve, H. Ueber Arachnodactylie, *Arch f Augenh* **104** 1-46 (May) 1931

7 Burch, F. E. Association of Ectopia Lentis with Arachnodactyly, *Arch Ophth* **15** 645-679 (April) 1936

revealed no abnormalities. In a few cases spina bifida occulta has been revealed roentgenographically.

The patient, as a rule, is moderately dolichocephalic. The large ears stand out prominently, the auricular cartilage is often imperfectly developed and gives poor support to the soft tissue. The face is long and thin, with a tendency to frontal bossing and prominence of the supraorbital ridges. The palate is high, and the teeth are sometimes irregularly placed. The jaw is long and often prominent and tends to droop, giving the subject a somewhat adenoid facies. The long face and glasses, which many of these children must of necessity wear, lend an air of premature senescence.

The eyes are deep set. The ocular defect when present is characteristic and a great diagnostic aid, but it should be emphasized that it is not necessary for the diagnosis. It consists of congenital bilateral dislocation of the lens, complete or incomplete and generally upward. When the lens is in the anterior chamber, glaucomatous phenomena are usually encountered. The lens itself shows a diameter that is less than normal, and it tends to be spherical, perhaps because the defective suspensory ligament no longer exerts its usual centrifugal force. Myopia is common, and vision is considerably impaired. The iris is left unsupported by the lens, consequently, tremulous wavy motions of the iris are noted when the patient turns his eyes rapidly from side to side. Unless obstructed by the displaced lens, the pupil is small and the reactions are limited, ostensibly owing to fibrosis of the iris rather than to a fault in the dilator muscle.

Probably as a result of the inadequate musculature and the ligamentous relaxation, spinal kyphosis and scoliosis of a marked degree of severity are common. Similarly the anterior portion of the chest is misshapen, with pigeon breast or funnel chest and asymmetry of the two halves of the thorax.

Infrequently, the patient becomes cyanotic or dyspneic on exertion and is limited in his activities on that account. A history of cardiac symptoms is not the rule, however. On examination the cardiac dulness may or may not be increased. In some cases there has been noted increased dulness to the left of the sternum in the second and third interspaces, and this increase in cardiac dimensions has been corroborated teleroentgenographically. Interpretation of the cardiac shadow on the roentgenogram is usually difficult, however, owing to the presence of scoliosis and consequent asymmetry of the chest with displacement of the heart. On auscultation, loud precordial systolic murmurs are common, in some cases loudest at the apex and in others at the base of the heart to the left of the sternum. More rarely, presystolic apical murmurs or diastolic murmurs heard along the left border of the sternum

have been described. These findings may suggest rheumatic heart disease, but three of the four patients who have come to autopsy have shown interauricular septal defects.

Finally, there is ordinarily a tendency to infantilism, with delayed development of secondary sexual characteristics, and often the basal metabolic rate is decreased. Values as low as -25 and -30 per cent have been recorded, but in view of the striking abnormalities of bodily configuration found in arachnodactyly, it seems likely that an element of error may enter the calculation of the metabolic rate when the findings are referred to the usual caloric tables based on height, weight and surface area.

The disease is hereditary and has been thought to be transmitted as a dominant mendelian characteristic. No definite racial proclivities have been described. The disease has, until lately, been known more generally to French and German physicians than to those of other countries, and therefore the majority of cases have been reported in families of European stock. Arachnodactyly occurs in the Negro, we have recently seen a Negro and three of his children, all with dislocation of the lens and other stigmas. The trait may be transmitted through either the mother or the father, consanguineous marriage was reported in few of the families. In the majority of instances stigmas of the syndrome have been noted in a parent or in brothers and sisters of the patient when the family was large, only a few cases have been reported as isolated instances in a family. The hereditary element becomes more apparent when it is realized that in large families formes frustes are the rule.

While it is not uncommon for all the major characteristics of the disease to be found in a single case, more often one or more of them are missing. Probably the most common abnormalities are the tall emaciated figure, the long slender fingers and the deformities of the spine and chest, these changes being noted in almost all cases. From combined statistics, the incidence of the other stigmas in patients with arachnodactyly is found to be somewhat as follows: ectopia lentis in 40 to 50 per cent, abnormalities of the external ear in 25 to 70 per cent and cardiac murmurs in 30 to 60 per cent. Thus, although such striking abnormalities as bilateral displacement of the lens or a loud precordial systolic murmur often are absent, the finding of long gracile extremities and other pronounced stigmas is considered sufficient for a diagnosis of arachnodactyly, particularly if the missing traits are present in other members of the family. The second of our two patients showed only the typical extremities and scoliosis, there was no familial history of symptoms of arachnodactyly other than that a first cousin had arachnodactylic fingers.

The fingers and toes are long at birth, and this feature is usually observed by the parents. The infant mortality for these patients is reputedly higher than it is for normal infants. Throughout childhood and adult life the arachnodactylic person has an inferior gross physical strength and is more often subject to infection of the upper respiratory tract and to other minor ailments. The intellectual faculties are normal. As the growing child begins to walk and become more active, the deformities of the spine and chest develop. When these are well established, they render intrathoracic disease additionally dangerous. Pneumonia in particular is a scourge and is the commonest cause of death among these patients.

The etiology of arachnodactyly is unknown and is vigorously debated. To early writers, before the hereditary nature of the disease was established, the characteristic findings of ligamentous relaxation and congenital heart disease suggested a similarity to mongolism. However, the theory of faulty gestation after maternal reproductive fatigue has been discredited. The arachnodactylic person is now generally recognized as a genetic sport, various mesodermal elements of the body structure having been affected in the early weeks of fetal life. Thus Weve⁶ would substitute the name congenital mesodermal dystrophy for the less comprehensive term arachnodactyly. There is discussion, however, as to whether a purely mesodermal fault could cause the defects often observed in the suspensory ligament of the optic lens. François,⁸ while considering the dystrophy mesodermal, regarded the hypophysis as its specific cause and suggested that it may be a form of fetal gigantism. Passow⁹ expressed the belief that the condition has a neurologic basis allied to that of syringomyelia, calling attention to the somewhat similar skeletal deformities noted in the so-called status dysraphicus sometimes associated with syringomyelia. Young⁴ observed that the symptoms of amyotonia congenita are occasionally associated with those of Marfan's syndrome, and he postulated a common origin for the two diseases.

The four patients that have come to autopsy offer no solution to the etiologic problem but corroborate the presence of cardiac and pulmonary abnormalities. Salle's¹⁰ patient, a 6 week old boy, had an enlarged heart with a hypertrophied right ventricle and a patent foramen ovale,

8 François, cited by Delord, E., and Viallefont, H. Luxation hereditaire du cristallin et syndrome de Marfan, *Bull. Soc. d'opht. de Paris*, January 1936, pp. 44-55.

9 Passow, A. Analogie und Koordination von Symptomen der Arachnodactylie und des Status dysraphicus, *Klin. Monatsbl. f. Augenh.* **94** 102-103 (Jan.) 1935.

10 Salle, V. Ueber einem Fall von angeborener abnormer Grosse der Extremitäten, *Jahrb. f. Kinderh.* **75** 540-550, 1912.

before death a loud systolic murmur was heard at the apex and in the pulmonic area. There was a bony exostosis on the floor of the sella turcica, but the hypophysis was normal save for a diffuse increase in the number of eosinophilic cells. Borger¹¹ reported an autopsy on a girl aged 1 year with physical findings typical of arachnodactyly, including a loud systolic murmur audible at the apex and at the base and transmitted all over the chest. Necropsy revealed that the heart was of normal size, with a patent foramen ovale. The middle lobe of the right lung was vestigial. In the anterior lobe of the hypophysis were several small cysts, and again the number of eosinophils seemed increased. The third patient, reported on by Piper and Irvine-Jones,³ was a girl of 21 months who had a systolic thrill and presystolic and systolic murmurs at the base of the heart. Autopsy revealed a deficiency in the interauricular septum. The middle lobe of the right lung was extremely small, the left lung consisted of a single lobe. The hypophysis was normal. A fourth patient, soon to be reported on by Rambau and Denenholz, had no congenital cardiac or pulmonary anomalies, and the hypophysis was considered normal.¹² The first three patients died of pneumonia, none showed a congenital abnormality of the cardiac valves.

In the absence of a satisfactory explanation as to the cause of the disease, treatment must be purely symptomatic. Orthopedic exercises and braces may ameliorate the various skeletal deformities, and successful removal of the dislocated lenses will, with proper correction, restore a fair degree of vision.

The two following cases of especial interest have recently been studied by us.

CASE 1—Skeletal findings typical of arachnodactyly. Acute rheumatic fever. Rheumatic heart disease with mitral insufficiency.

F. K., a 12 year old boy, was admitted to the medical service of the Johns Hopkins Hospital in September 1936, complaining of articular pains and epigastric discomfort. His mother, an emigrant from Ukraine, had died at the age of 37 of a renal disorder. It was reported that she had long fingers and toes, a hunched back and normal eyesight. The patient's father and one brother were normal. At birth the patient was noted to have long fingers and toes. At the age of 2½ years he was brought to the pediatric dispensary with Sydenham's chorea and was described as tall and undernourished. There was lateral curvature of the spine but no thoracic deformity. The heart was enlarged to the left, with a precordial systolic murmur loudest at the apex. The boy survived the chorea and two subsequent attacks of pneumonia but continued to be frail and suffered frequently from otitis media. He was able to maintain a creditable standing at a rural school but was clumsy and not proficient at sports. There was no complaint of dyspnea or cyanosis, and vision was normal. He was admitted to the hospital at the age of 12 in his second attack of polyarthritis in three years.

11 Borger, F. Ueber zwei Fälle von Arachnodaktylie, *Ztschr. f. Kinderh.* 12: 161-184, 1915.

12 Dr. Rambau has given us permission to include this case in our series.

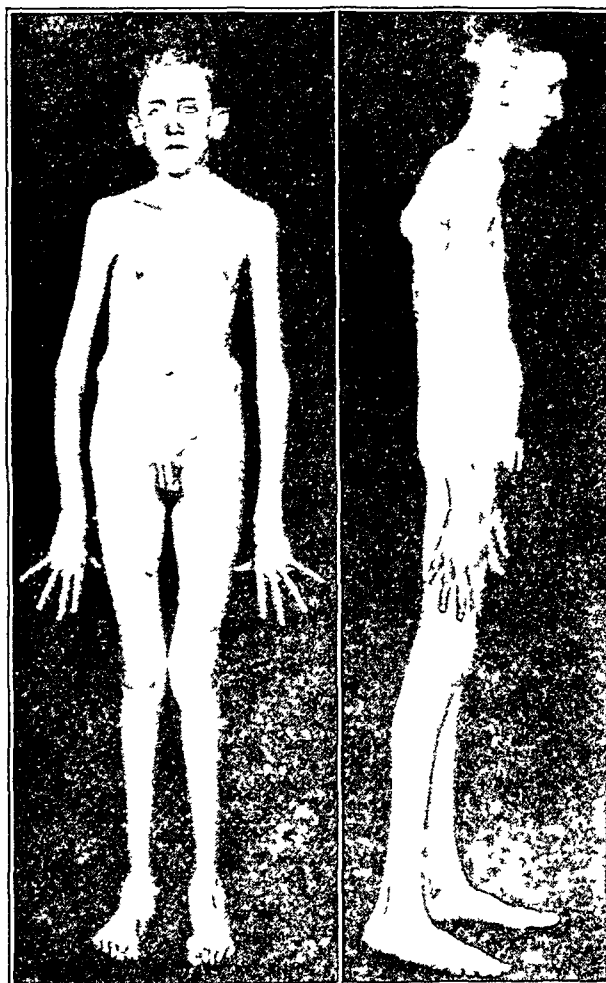


Fig 1 (case 1) —Patient with arachnodactyly

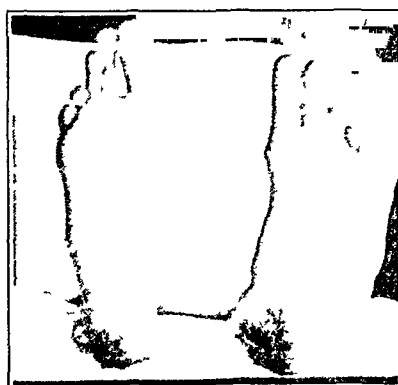


Fig 2 (case 1) —Feet of a patient with arachnodactyly

On admission to the hospital he had obvious acute rheumatic fever, with a temperature of 101.2 F, a pulse rate of 132 and typical subcutaneous rheumatic nodules over the knees and elbows. He was tall, gaunt and emaciated (height, 63¾ inches [162 cm], weight, 71 pounds [32 Kg]). The fingers and toes were extraordinarily long, slender and slightly webbed. There was marked thoracic scoliosis to the right, with flattening of the right anterior portion of the chest and depression of the sternum. He walked awkwardly with inturned toes, there were bilateral pes planus and hallux valgus. The musculature was poorly developed but without evidence of amyotonia. The patellar ligaments were lax. The boy was dolichocephalic, with a long face and projecting ears.

Examination of the eyes by Dr. E. Burch revealed no abnormality other than a slight refractive error.

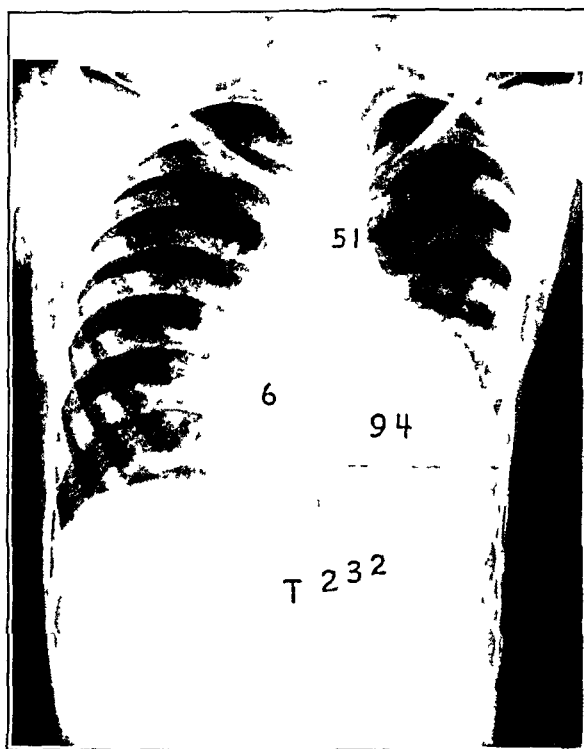


Fig. 3 (case 1) —Teleroentgenogram of a patient with arachnodactyly

The heart was greatly enlarged, with the apical impulse in the posterior axillary line. The first sound at the apex was loud, and the second pulmonic sound was accentuated. There was a marked apical systolic thrill, and the accompanying murmur, though audible all over the precordium, was most loud and rough at the apex. Diastole was everywhere clear. The heart shifted well with a change of the patient's position.

The abdomen was not remarkable, the testes were in place in the scrotum and neurologic examination showed nothing abnormal.

The urinalysis and blood counts were normal save for mild anemia, the Wassermann reaction of the blood was negative. The calcium content of the serum was 10.2 mg per hundred cubic centimeters. The basal metabolic rate was +20 per cent.

In the electrocardiogram the P wave was large, and in lead III it was biphasic.

Roentgenograms showed that the sella turcica was slightly smaller than normal. The cardiac measurements were valueless because of thoracic scoliosis,

but there was definite prominence in the region of the pulmonary conus and left auricle. The extremities were normal save for the unusual length and slimmness of the phalanges, metacarpals and metatarsals.

After rest in bed and treatment with acetylsalicylic acid and digitalis the attack of rheumatic fever subsided, and the patient returned to school in four months. He returned to the hospital in August 1937 in myocardial failure and died. Permission for autopsy was not obtained.

CASE 2—*Typical skeletal evidence of arachnodactyly Pyopneumothorax*

D. K., a 13 year old girl, entered the hospital in March 1936, complaining of pain in the right side of the chest. The family was of German descent. The parents and a younger brother were normal, but a first cousin on the maternal side had unusually long mobile fingers and had had two attacks of rheumatic fever,



Fig. 4 (case 2) —Showing the hypermobility of the joints in arachnodactyly

without evidence of cardiac involvement. At birth the patient was noted to have long fingers and toes and a pigeon breast, later scoliosis developed. She was always thin and underweight, but her health otherwise was excellent. She was active and enjoyed sports, capitalizing her double-jointedness for the amusement of her friends. Her school record was excellent. There were no ocular or cardiac complaints. Four weeks previous to her admission to the hospital pneumonia developed, and when the fever did not subside after eleven days, the physician tapped the right side of the chest. While the needle was still in place, she experienced sharp pain and became short of breath. She continued to have fever and pain in the right side of the chest.

On admission to the hospital she appeared acutely ill, pale and undernourished. There were a spiking fever and typical signs of hydropneumothorax on the right. She was exceedingly thin, weighing only $71\frac{1}{2}$ pounds (32.5 Kg.) and being 60 inches (152.5 cm.) tall, and had little subcutaneous fat. The extremities were

long and gracile, and the spidery fingers and toes presented an extraordinary appearance. There was remarkable hypermobility of all the joints, enabling her to perform such double-jointed feats as laying the shaft of the thumb flat along the radius with the wrist either flexed or extended. The skull was dolichocephalic, and the ears were prominent.

Examination of the eyes by Dr. E. Burch showed that they were essentially normal.

There were mild dorsal scoliosis to the left and pronounced pigeon breast. The heart was displaced to the left but otherwise normal. Secondary sexual characteristics were just beginning to develop.

The urinalysis and blood count were normal save for mild anemia and moderate leukocytosis associated with the infection. The Wassermann reaction of the blood was negative. Hydropneumothorax on the right was demonstrated roentgenographically, with loculation of the fluid, the heart appeared normal. Culture of the fluid aspirated from the chest showed *Haemophilus influenzae* and later *Bacillus coli communis*.

After a prolonged febrile course, rib resection was performed, and the child was discharged in good health after three and a half months in the hospital.

COMMENT

These reports are of interest not only because they exemplify arachnodactyly without ectopia lentis but because they describe instances of two medical conditions the association of which with arachnodactyly is perhaps of some significance. The first child had such obvious evidence of rheumatic infection elsewhere that the cardiac signs were attributed to mitral insufficiency, with possible early stenosis, even though underlying congenital heart disease was possible. It is interesting that three of Burch's eight patients were said to have had rheumatism. In one case a diagnosis of chronic adhesive pericarditis was made, in another there was a history of accentuation of cardiac symptoms after an attack of chorea, with the physical signs of mitral stenosis and aortic insufficiency, and in the third the physical signs of a double valvular lesion were present. In addition, the cousin of our second patient, who had stigmas of arachnodactyly, had had rheumatic fever in the past. Roesler,¹³ in his review of hearts which showed as the chief congenital defect an interauricular septal defect greater than 1 cm., found that in 77.4 per cent there was also chronic valvular disease, probably of rheumatic origin. Since patency of the interauricular septum is the commonest cardiac anomaly in arachnodactyly, an increased incidence of rheumatic fever in these cases becomes possible. However, the problem of the differential diagnosis between congenital cardiac anomalies and possible superimposed rheumatic endocarditis is of course so difficult that without a considerable series of autopsies no definite conclusions can be reached.

¹³ Roesler, H. Interatrial Septal Defect, *Arch. Int. Med.* **54**: 339-380 (Sept.) 1934.

The second child, with pyopneumothorax, may be considered as demonstrating the well substantiated proclivity to pulmonary disorders shown by patients with Marfan's syndrome. The susceptibility of these patients to pneumonia is constantly referred to in the literature. The thoracic deformities, the anomalies in the arrangement of the lobes and the general frailty of these patients are usually given in explanation. It seems logical that these characteristics should tend to make the disease more grave and its complications more frequent.

SUMMARY

Two cases of arachnodactyly are reported with associated intrathoracic disease, in the first case rheumatic endocarditis being present and in the second case pyopneumothorax. The frequency of pneumonia in association with this syndrome is emphasized, and it is remarked that a number of the patients have had rheumatic fever. The characteristics of arachnodactyly from a general medical standpoint are reviewed, and it is pointed out that the better known ophthalmologic complications occur only in about half the cases and are not necessary for the diagnosis.

THE HEART IN ACROMEGALY

CYRIL COURVILLE, M D

AND

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LOS ANGELES

The striking alterations of the skeletal, muscular, dermal and nervous systems produced by a chromophilic adenoma of the pituitary body have been adequately described by many observers. The changes produced in the cardiovascular system of patients with acromegaly, although the direct cause of death in the majority of instances, have been infrequently described and insufficiently studied. We have been impressed by the frequency with which weakness, syncope and the more common symptoms of cardiac failure have dominated the terminal clinical course in these cases. This circumstance has often been neglected because attention has been fixed on the more spectacular features of the disease, especially the surgical aspects. On this account, recent medical reports usually fail to describe adequately the changes in the cardiovascular system. We have had occasion to study a small number of patients with acromegaly with reference to the cardiovascular system both during life and at postmortem examination, and the results of these observations are embodied in this report.

The cause of the death of a patient with acromegaly, in the absence of intracranial complications, diabetes mellitus or a surgical procedure, is a subject of considerable interest. The progressive enfeeblement of the musculature and the ultimate onset of shortness of breath on the least exertion are in striking contrast to the appearance of great physical strength presented by these patients. This strange contrast was mentioned by Carlyle in his work entitled "History of Frederick the Great" and is known to all those who have watched the progress of the disease when unmodified by surgical or roentgen treatment.

Huchard,¹ in 1895, reported his studies of three acromegalic patients, with autopsy records. He stated that cardiomegaly might be part of general splanchnomegaly, it might be dependent on general arteriosclerosis

From the Los Angeles County General Hospital

Presented in abstract before the Association of American Physicians, May 5, 1936

1 Huchard, H. Anatomie pathologique, lesions et troubles cardio-vasculaires de l'acromegalie, J d praticiens 9 249, 1895

or it might be caused by deformity of the spine and of the thoracic cage. He submitted his theories to Pierre Marie, who suggested that in acromegaly there might be great hypertrophy of the whole cardiovascular system and also hypertrophy of the elements of the sympathetic nervous system.

The best and earliest collected review was published by Fournier,² in 1896. He studied twenty-five collected records and called particular attention to the clinical picture of heart failure in these cases. He emphasized the importance of easy fatigability, leading to extreme asthenia, combined with periods of syncope which often preceded the appearance of symptoms of grave heart failure. These symptoms were often associated with cardiomegaly and general splanchnomegaly, with the characteristic kyphotic deformity of the chest, with the high position of the heart and with variable degrees of arteriosclerosis.

Paviot and Beutter,³ in 1904, described the large heart and the hypertrophy of the individual muscle fibers of an acromegalic patient who died of heart failure. Labadie-Lagrave and Deguy⁴ and Alessandri⁵ published records of two acromegalic patients with large hearts. One of these patients had hypertension, and the other had a saturnine nephropathy. Humphry and Dixon,⁶ in 1910, studied an acromegalic patient with a large heart, marked splanchnomegaly and heart failure associated with moderate hypertension. They said they believed that they found a pressor substance in the urine. The heart at autopsy weighed nearly 1,300 Gm. Lubarsch,⁷ in 1912, and Grellier,⁸ in 1914, discussed this phase of acromegaly in brief articles. Amsler,⁹ in 1912, discussed the theories of splanchnomegaly in acromegaly and concluded that the cardiac hypertrophy was hormonal in origin rather than secondary to certain other features of the disease, such as arterial hypertrophy,

2 Fournier, J. B. C. *Acromegalie et troubles cardio-vasculaires*, Thesis, Paris, no 111, 1896.

3 Paviot, J., and Beutter, M. *Acromegalie, splanchnomegalie, gros coeur, mort par asystolie*, *Lyon med* **36** 1088, 1904.

4 Labadie-Lagrave and Deguy. *Associations morbides de l'acromegalie*, *Arch gen de med* **1** 129, 1899.

5 Alessandri, G. *Acromegalia con polso raro permanente ed enorme ipertensione arteriosa*, *Polichinico (sez prat)* **15** 913, 1908.

6 Humphry, L., and Dixon, W. E. *A Case of Acromegaly with Hypertrophied Heart. Pressor Substances in the Urine*, *Brit M J* **2** 1047, 1910.

7 Lubarsch, O. *Hypophyse und Akro- und Splanchnomegalie*, *Jahresk f arztl Fortbild* **3** 70, 1912.

8 Grellier, G. *L'appareil circulatoire au cours de l'acromegalie*, Thesis, Paris, no 441, 1914.

9 Amsler, C. *Zur Lehre der Splanchnomegalie bei Akromegalie*, *Berl klin Wchnschr* **2** 1600, 1912.

kyphosis and splanchnomegaly Eltester and Schroeder,¹⁰ in 1914, discussed the problem of splanchnomegaly and reviewed the cardiovascular symptoms in acromegaly Bassoe¹¹ stated that in acromegaly there is general dilatation of the blood vessels, with sclerosis and adrenal hyperplasia, and that a pressor substance is present in the blood He said he believed that these factors are of prime importance in the production of cardiac hypertrophy

A few of the monographs dealing with acromegaly have discussed the alterations of the cardiovascular system Sternberg¹² stated that splanchnomegaly undoubtedly belongs to the phenomena of the disease

By certain authors (Klebs, Dallemagne, Huchard) the increase of the size of the heart so frequently observed is considered as belonging to it The vessels, especially the arteries, are, as a rule, dilated and thickened The thickening affects all three coats True atheromatous changes may exist or may be altogether absent The changes in the vessels extend from the aorta and pulmonary artery up to the fine ramifications in the organs as already described in connection with the skin Examination of the thickened vessels shows increase of the endothelium of the intima, decrease of the musculature and compensation by the cellular tissue, and increase of the adventitia According to Klebs, the dilatation is the primary, the active phase of the process, and the cellular tissue hyperplasia of the intima, with the consequent narrowing of the vessels, a secondary occurrence Much may be said for the opposite opinion, that the dilatation is the secondary process, a result of the atrophy of the muscular and elastic tissue, and of their replacement by new-formed cellular tissue The heart is, as a rule, enlarged—atrophy is described only by Henrot—especially dilatation and hypertrophy of the left ventricle As in almost all cases, disease of the vessels just described was present, the changes in the heart may be, without difficulty, conceived as a natural result Virga, Sigurini and Caporiacco have seen congenital narrowness of the aorta

Steinberg also described the changes in the skin as follows

The small vessels at once attract notice owing to the thickness of their walls and dilatation The enlargement and affection of the heart may be, according to Huchard, accounted for in three ways (1) by the splanchnomegaly, (2) by the arterial sclerosis, (3) by the alteration in shape of the cavity of the chest Very frequently the sufferers show signs of insufficient cardiac action The colour of the face is more or less cyanotic, a certain amount of dyspnoea is always suffered from The general feebleness of the body, which is seldom wanting as the disease advances, is partly of cardiac action Fainting fits are frequent The disturbance of the circulation may be the most prominent condition in the disease the patient becoming more and more dyspnoeic, finally oedematous, at last confined to his bed, and sinks from cardiac failure

10 Eltester and Schroeder Ueber einen Fall von Akromegalie und Splanchnomegalie, *Med Klin* 10 1311, 1914

11 Bassoe, P Acromegaly, in *Endocrinology and Metabolism*, New York, D Appleton & Company, 1922, vol 1, p 805

12 Sternberg, M Acromegaly, translated by F R B Atkinson, London, H K Lewis, 1899

Marie and Souza-Leite¹³ stated

With regard to the vascular system, important changes have been noted. The heart is increased in size. This hypertrophy was more marked in Freund's case than in that of Erb, in whose patient a systolic bruit was heard at the apex.

Hinsdale¹⁴ also discussed the subject. He stated

The lesions of the vascular system present three phases—dilatation of the vessels, thickening of the walls, and obliteration of their lumen. In the first instance, there is a simple cardiomegaly, accompanied exceptionally with insufficiency of the cardiac valves. In the second, there is a true sclerotic myocarditis, a cardio-renal arteriosclerosis with what he (Fournier) terms a hyposystole, a cardiac liver with edema of the feet and albumen in the urine. Thus the heart participates in the general growth. In Osborne's case it weighed 39 ounces.

Cushing and Davidoff¹⁵ reported the microscopic alterations of the heart of one of their patients as follows:

Histologically, the muscle fibers appear to be greatly enlarged and the supporting connective tissue markedly and diffusely increased. There are occasional scarred patches in which atrophic muscle fibers are seen. The larger blood vessels show some intimal thickening, the smaller ones are unaltered.

In this instance there was marked splanchnomegaly. The heart weighed 1,050 Gm. and presented concentric hypertrophy with little dilatation. This patient died of heart failure. These authors also discussed the heart in acromegaly as follows:

The largest recorded heart was also in Osborne's case, with the amazing weight of 1275 grams, the next largest was in our Case 1 of 1050 grams, the next in Case 3 of 1000 grams. These weights, needless to say, have been taken with the hearts emptied. Osborne's patient died of cardiac failure, just as did our Case 3, but this is not true of Case 1 which, of the two, had the larger heart. In Kraus's case, the heart weighed 950, in Widal's, 875, and in Paviot and Beutter's, 830 grams, the only other examples exceeding 500 grams. Several writers have been particularly struck by the absence of valvular disease or arteriosclerosis to which the huge hearts sometimes seen in acromegalics might be ascribed.

It is apparent that many theories may be formulated to explain the cardiac hypertrophy and eventual cardiac failure in this disease. A few of these may be profitably discussed at this point:

1. In the majority of these cases of cardiac hypertrophy and splanchnomegaly the size of the heart is out of proportion to the size

¹³ Marie, P., and Souza-Leite. *Essays on Acromegaly*. London, Adlard & Son, 1891.

¹⁴ Hinsdale, G. *Acromegaly*, Detroit, W. W. Warren, 1898.

¹⁵ Cushing, H., and Davidoff, L. M. *The Pathological Findings in Four Autopsied Cases of Acromegaly, with a Discussion of Their Significance*, Monograph 22, Rockefeller Institute for Medical Research, 1927.

of the patient or to his muscular development. It is necessary therefore to explain the cardiac hypertrophy by some other mechanism than general overgrowth of the individual with acromegaly, and, in addition, it is desirable to demonstrate that the hypertrophy is a "work hypertrophy." In the absence of hypertension, pericardial disease, marked arteriosclerosis, valvular disease, an increased basal metabolic rate or histologic evidences of progressive myocardial disease, no theory based on so-called work hypertrophy due to these particular causes can be sustained.

2 The cardiac hypertrophy in acromegaly is not causally related to an increased intracranial pressure, to diabetes mellitus or to an increased basal metabolic rate.

3 Although comparable statistics are not available, one can assume with reasonable certainty that the cardiac failure in acromegaly does not follow the general age curve of heart failure with advancing age. We believe that it is probably more directly related to the duration and the severity of the acromegalic process.

4 We are not of the opinion that the characteristic deformity of the chest, with displacement of the heart upward, plays any but a minor role in producing the cardiac hypertrophy and failure.

5 A review of the protocols of our cases clearly demonstrates that the causal factor did not originally lie in the heart itself. We have reviewed the sections of cardiac muscle from acromegalic patients who died of heart failure and from a series of patients with cardiac hypertrophy due to other causes, excluding obvious disease of the coronary artery. There is no constant histologic alteration present in the myocardium which distinguishes the enlarged acromegalic heart from other enlarged hearts. The factors we noted were fragmentation, fibrosis, cellular infiltration, the size of the muscle fibers and arteriosclerosis. Photomicrographs of these sections at a constant magnification have been studied with considerable care. No constant change could be found which would allow us to state which was and which was not the heart of a patient with acromegaly. Hypertrophy of the muscle fibers, which has been stated to be the cause of cardiomegaly in acromegaly, is not a constant finding, as a matter of fact, the largest, as well as the smallest, muscle fibers which we found were noted in the hearts of patients with acromegaly who had died of heart failure. When compared with muscle fibers of normal hearts or large hearts of patients without acromegaly, the muscle fibers of a large acromegalic heart may actually be smaller than normal. This fact only demonstrates again the absence of any correlation between the size of the muscle fiber of

the heart and its functional capacity. It may be assumed that hypertension, valvular heart disease and arteriosclerosis are not related in any way to the cardiac hypertrophy of acromegaly, in spite of the fact that in acromegaly the blood vessels are enlarged, both as to the thickness of the walls and as to the size of the lumens. It is our belief, therefore, that these factors are of little importance in the ultimate cardiac failure.

When all these factors are considered and given their proper significance, according to present knowledge, it may be concluded that in acromegaly, as in other types of cardiac enlargement, the hypertrophy is dependent on an increased "work demand" on the heart. It is probable that cardiac hypertrophy occurs first to compensate for the abnormal growth of the patient and to meet the increased demands occasioned by the general splanchnomegaly which is constantly present in acromegalic patients with heart failure. The abnormal growth of the patient, which is the important physiologic result of the hormonal disturbance produced by the eosinophilic adenoma, either directly or indirectly, leads to general muscular weakness and probably to cardiac muscular weakness. Thus the cardiac muscle, stimulated by hormonal influence to abnormal growth as regards either size or number of poorly functioning muscle cells, reaches the stage of diminishing cardiac reserve, which it attempts to meet by further hypertrophy. This hormonal theory in the present state of knowledge more nearly takes into account all the known circumstances and exceptions than any of the other theories which have been propounded.

An elevation of the basal metabolic rate has been observed in cases of eosinophilic adenoma of the pituitary body, first by Magnus-Levy¹⁶ and subsequently by a large number of observers. It has been discussed by Davidoff,¹⁷ Cushing and Davidoff¹⁸ and Davis.¹⁹ Anderson and Collip²⁰ have obtained an active thyrotropic substance from the anterior lobe of the pituitary body. It seems reasonable to assume that, in addition, an organotropic hormone must be present to produce the splanchnomegaly so frequently present in acromegaly. However, an elevated

16 Magnus-Levy, A. Untersuchungen zur Schilddrüsfrage, *Ztschr f klin Med* **33** 269, 1897.

17 Davidoff, L. M. Studies in Acromegaly. The Anamnesis and Symptomatology in One Hundred Cases, *Endocrinology* **10** 461, 1926.

18 Cushing, H., and Davidoff, L. M. Studies in Acromegaly. IV. The Basal Metabolism, *Arch Int Med* **39** 673 (May) 1927.

19 Davis, A. C. The Thyroid Gland in Acromegaly, *Proc Staff Meet, Mayo Clin* **9** 709, 1934.

20 Anderson, E. M., and Collip, J. B. Thyrotropic Hormone of Anterior Pituitary, *Proc Soc Exper Biol & Med* **30** 680, 1933.

basal metabolic rate is present in about 50 per cent of the cases of acromegaly. It is not a constant finding in cases of acromegaly with heart failure or in cases of acromegaly with marked splanchnomegaly. It should also be stated that the elevated metabolic rate is not always satisfactorily reduced by thyroidectomy or by iodine therapy.

We are inclined to believe that in the period of overactivity of the anterior lobe, the basal metabolic rate may be increased, but whether this is due to the hormone of the pituitary body, to the increased splanchnomegaly produced by this hormone or to some influence on the thyroid gland is not known. It is apparent that this manifestation of the disease needs further statistical study for its complete elucidation. We feel certain that the increased basal metabolic rate is of minor and probably negligible importance in the ultimate production of heart failure.

We have had the opportunity to study twenty-four patients with acromegaly for periods varying from a few months to over ten years. At the Los Angeles County Hospital there has been about one acromegalic patient for every ten thousand patients admitted. Of these twenty-four patients, ten were women. The ages varied from 25 to 60 years, the average being 48 years. The average age at death of those who died of heart failure was 48 years. The average age at the time of observation of all who had definite heart failure was 48 years. Of the twenty-four patients, eighteen had definite evidence of heart failure, and of this group, six have died of heart failure. At autopsy the hearts of these patients weighed 500, 400, 1,140, 1,200, 840 and 500 Gm, respectively. Three other patients of the entire group have died as a result of hemorrhage into the pituitary adenoma (heart weight, 500 Gm), diabetic coma (heart weight, 280 Gm) and psittacosis (heart weight, 540 Gm), respectively. The basal metabolic rates for the group were not determined as a routine. One patient in early diabetic acidosis had a rate of +27 per cent. One patient without cardiac symptoms had a rate of -18 per cent. The rates for ten patients with varying degrees of heart failure were -12, +19, -9, -12, -18, +7, +14, +18, +28 and -1 per cent, respectively. A discussion of the significance of alterations of the basal metabolic rate may be found in the articles by Cushing and Davidoff¹⁸ and Davis.¹⁹

There have been reported a number of instances of acromegaly and high blood pressure. Whether there is any causal relation between the two seems doubtful. In one of the patients in this group, a patient aged 50 with severe diabetes, hypertension developed during observation, and death resulted from heart failure. Another, aged 57, who died of cardiac failure, had a blood pressure of 150 systolic and 100

diastolic Another, aged 56, had a pressure of 170 systolic and 90 diastolic For the remainder the blood pressure was normal or slightly below normal

Roentgenograms of the sella, the fingers and the heart, as well as perimetric observations, were made in nearly every instance and did not differ from those reported by other observers It is of some interest that in this group of patients, none of whom had had any surgical procedure directed toward the pituitary adenoma, there was no instance of serious loss of useful vision

The manifestations of disease presented by patients with acromegaly are so varied that they will not be discussed in their entirety at this time We shall limit our remarks to those features of the disease which are associated in general with cardiac weakness and ultimate cardiac failure

Weights, in Grams

Case	Heart	Lungs	Liver	Spleen	Kidneys	Thyroid	Brain
1	500	1,640	3,060	240	580	60	1,460
2	840		2,820	480		660	
3	2 times normal		Large	3 times normal			
4	1,200		2,650	265	675		1,340
5	280		2,900	260			
6	1,140	3,890	4,150	450	740		
7	400		1,900	430	380		
8	540		2,200	300	560		

It is well known that progressive weakness ultimately appears in patients with acromegaly if the active phase of the disease is sufficiently prolonged In a few, after reaching a certain degree of intensity, the acromegalic features cease progressing, and the disease becomes quiescent In a certain proportion of patients diabetes mellitus makes its appearance, and the patient may eventually die in diabetic coma In the majority of all patients with acromegaly, symptoms referable to the heart eventually become the most striking clinical phenomena In not a few cases the acromegalic changes may be meager, and the patient presents himself on account of headache, palpitation and breathlessness on exertion

One of our patients had a basal metabolic rate of $+18$ per cent The heart was large, and he complained of headache and breathlessness Thyroidectomy had been advised However, on careful study it was found that he had no apparent abnormality of the thyroid gland but that he did have a large liver and a large spleen Roentgenographic examination of the fingers and sella and perimetric studies of the visual fields confirmed the diagnosis of acromegaly It is certain in this

instance that the splanchnomegaly preceded the development of the more usual acromegalic changes, and instances of this sort confirm our belief that the hormonal action on the heart is the primary factor in the ultimate production of heart failure, not the skeletal, muscular, dermal or vascular overgrowth. This patient was treated vigorously with roentgen rays, and the splanchnomegaly and the symptoms of heart failure disappeared.

A second patient presented himself on account of an unproductive cough. On examination the lungs appeared normal, but the heart, liver and spleen were enlarged. No cause for the cardiac enlargement could be determined. The patient showed few of the usual symptoms of acromegaly, but examination of the bones and of the sella roentgenographically showed the characteristic changes of acromegaly. The cough was probably dependent on enlargement of the larynx. The shortness of breath on exertion, of which he complained, was greatly relieved by roentgen therapy.

In general, the first symptom complained of by these patients is weakness. This weakness, of course, is in striking contrast to the great muscular development. As the symptoms increase, the weakness and easy fatigability are augmented by palpitation and breathlessness on exertion. Soon attacks of syncope make their appearance, and the patient becomes practically an invalid. As the disease progresses a striking pallor appears, asthenia becomes extreme, breathlessness becomes constant, the pulse becomes rapid and irregular and the patient succumbs to heart failure.

A few individual symptoms and signs may now be discussed. 1 Hypertension is not a feature of acromegaly and in our opinion is not produced by acromegaly. When present it should be looked on as a coincidental disease. 2 Valvular disease of the heart when present in patients with acromegaly is also probably due to some other disease. 3 Hypertrophy of the heart is always present in patients with acromegaly and heart failure. The heart may be of enormous size. In one of our cases the heart weighed 1,200 Gm. 4 The electrocardiographic changes are neither constant nor specific. There is usually evidence of left axis deviation, and as the disease progresses, changes of the QRS complex, usually with broadening and slurring and at times notching and widening, point to disturbances of impulse conduction due to diffuse myocardial damage. Later, various arrhythmias may make their appearance, and in the later stages significant changes of the T wave may appear.

In the terminal stages of the disease the symptoms of heart failure differ little from those seen in other types of heart failure. The rapid or irregular pulse can no longer be slowed with moderate doses of digi-

talis, breathlessness and orthopnea become marked, cyanosis is striking, edema, pulmonary congestion and Cheyne-Stokes respiration appear and the patient ultimately dies of heart failure

SUMMARY

This report is based on the observations of twenty-four patients with acromegaly. Of this group, eighteen (75 per cent) presented evidence of marked heart failure, and six have died of heart failure. These six patients all had marked splanchnomegaly and cardiomegaly, and an eosinophilic pituitary adenoma was observed post mortem.

CHOLESTEROL CONTENT OF THE BLOOD IN HEART DISEASE

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AND

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To the steadily increasing number of studies of cholesterol in the blood in various clinical entities reported in the literature, we now add our investigation on the concentration of this lipid in the blood in heart disease

MATERIAL AND METHODS

The subjects used in this study were chosen at random from the group of patients who had been attending the cardiac clinic for adults of the New York Post-Graduate Hospital for at least one year and for whom the etiologic diagnosis was reasonably certain. When the conditions were classified functionally according to the standards of the New York Heart Association, the cases fell, for the most part, into classes 2a and 2b, with an occasional case belonging to either class 3 or class 1. A total number of sixty-one patients were studied, eighteen of whom had rheumatic heart disease, twenty-four had arteriosclerotic heart disease and nineteen had hypertensive heart disease, the patients with hypertension also manifested some evidence of arteriosclerosis. A group of thirty-three normal subjects was used for comparative study.¹

Only single studies of the blood were carried out, venipuncture being done between 2 and 3 p m. No attempt was made to determine the amount or type of food previously consumed, since it has been shown that the ingestion of food does not alter appreciably the cholesterol content of the blood.² The total cholesterol and ester cholesterol contents were determined for the plasma by the Bloor-Knudson³ procedure, modified with temperature control as practiced in this laboratory.⁴

Aided by a grant from the Harriet Weil Fund

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1 The normal subjects had been studied in this laboratory by means of the same analytic procedures used in the present investigation (Hartung, E F, and Bruger, M. The Cholesterol Content of the Plasma in Arthritis, *J Lab & Clin Med* **20** 675, 1935)

2 Bruger, M, and Somach, I. The Diurnal Variations of the Cholesterol Content of the Blood, *J Biol Chem* **97** 23, 1932

3 Bloor, W R, and Knudson, A. The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, *J Biol Chem* **27** 107, 1916

4 Mirsky, I A, and Bruger, M. A Note on the Liebermann-Buchard Color Reaction for Cholesterol, *J Lab & Clin Med* **18** 304, 1932

RESULTS

In order to conserve space the individual results will not be detailed. As shown in the accompanying chart, the patients with rheumatic heart disease tended to have a lower concentration of cholesterol in the blood than those with either arteriosclerotic or hypertensive heart disease. Thus, it will be observed that whereas 28 per cent of the patients with rheumatic heart disease had blood cholesterol values below 150 mg per hundred cubic centimeters, not one of the patients with either arteriosclerotic or hypertensive heart disease exhibited a similar hypocholesteremia. Again, it will be noted that whereas only 5 per cent of the

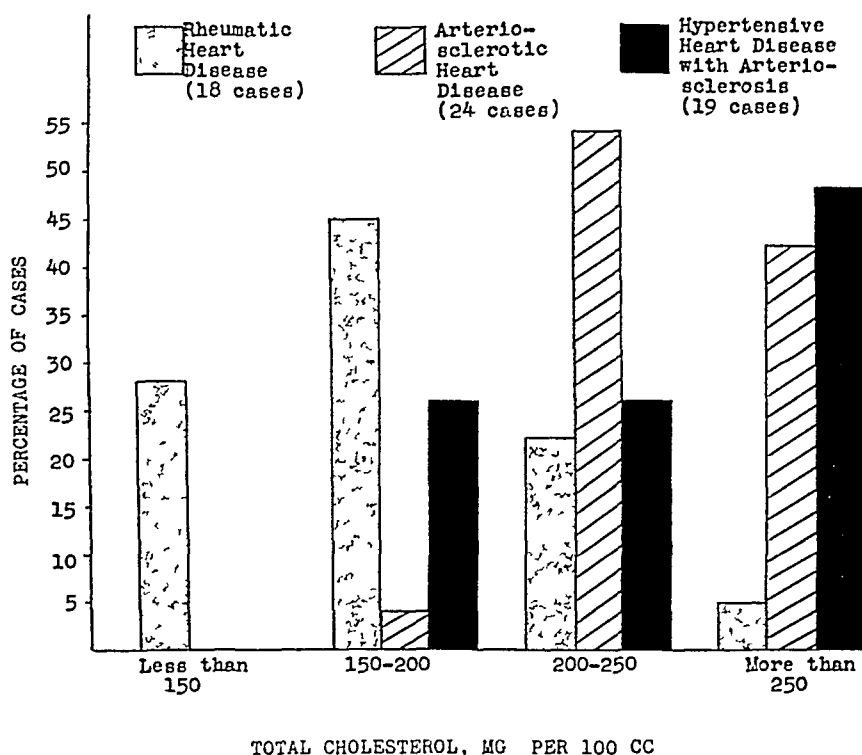


Chart showing the frequency distribution for total plasma cholesterol for patients with heart disease

patients with rheumatic heart disease showed a concentration of cholesterol in the blood over 250 mg per hundred cubic centimeters, approximately 45 per cent of the patients with either arteriosclerotic or hypertensive heart disease demonstrated this hypercholesteremia. Although a noteworthy difference as to the concentration of the cholesterol in the blood existed between patients with rheumatic heart disease, on the one hand, and those with arteriosclerotic or hypertensive heart disease, on the other, little or no difference could be observed as to the distribution of the blood cholesterol values when the patients with arteriosclerotic and those with hypertensive heart disease were compared.

The results are treated statistically in the accompanying table. The arithmetical means indicate the trend, the cholesterol content of the plasma tended to be low in rheumatic heart disease and elevated in arteriosclerotic or hypertensive heart disease. The results for the group with rheumatic heart disease were not significant on a statistical basis, since the difference between the means for the group of normal subjects and those for the group with rheumatic heart disease divided by the standard error of the difference of these means gave a value of only 1.03. However, when the same calculations were employed for the groups of patients with arteriosclerotic and with hypertensive heart disease, the results were 4.9 and 4.29, respectively, values that are statistically significant.

The Total Cholesterol Content of the Plasma of Normal Subjects and of Patients with Heart Disease—Statistical Analysis

Group	Number of Observations	Arithmetical Mean, Mg per 100 Cc	Standard Deviation*	Probable Error of Mean†	$\frac{d \pm}{\sigma D}$
Normal	33	195	29	3.42	
Rheumatic heart disease	18	185	35	5.56	1.03
Arteriosclerotic heart disease	24	248	47	6.48	4.90
Hypertensive heart disease with arteriosclerosis	19	246	47	7.27	4.29

* Standard deviation $\sigma = \sqrt{\frac{\sum (d^2)}{N}}$ $\sum (d^2)$ represents the summation of the squares of the individual deviations from the mean and N the number of determinations.

† Probable error of mean $= 0.6745 \frac{\sigma}{\sqrt{N}}$ σ represents the standard deviation and N the number of determinations.

$\pm \frac{d}{\sigma D}$ represents the difference between two means divided by the standard error of the difference. The standard error of the difference, σD , is calculated from the formula $\sigma D = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$ σ_1 and σ_2 represent the standard deviations for the two groups, and N_1 and N_2 represent the number of determinations for the two groups.

No appreciable difference was observed in the ratios of ester to free cholesterol in the three major types of heart disease considered. For patients with rheumatic heart disease the average ester-free ratio was 1.7, for those with arteriosclerotic heart disease, 1.86, and for those with hypertensive heart disease, 1.77.

COMMENT

It is generally known that patients with rheumatic heart disease fall into a decidedly lower age group than those with either arteriosclerotic or hypertensive heart disease, and it may be inferred that the observed differences in the cholesterol content of the blood in the various types of heart disease may be due to the age factor. Parhon and Parhon⁵

⁵ Parhon, C. J., and Parhon, M. L'hypercholesterinémie de la vieillesse, *Compt. rend. Soc. de biol.* **88** 231, 1923.

have maintained that there is a slight increase in the blood cholesterol content with advancing years in human beings, in persons over 70 years of age they frequently observed definite hypercholesteremia. However Gorham and Myers⁶ reported that the blood cholesterol values for fourteen normal subjects, 3 of whom were 51, 65 and 55 years old, respectively, ranged from 130 to 170 mg per hundred cubic centimeters. In a recent detailed study on the plasma lipid content for normal men at different ages, Page and his associates⁷ demonstrated that variations of age from 20 to 90 years do not have a determinable influence on either the amount or the composition of the plasma lipids. Differences in age distribution, therefore, apparently fail to account for the variations in the level of the blood cholesterol noted in the various types of heart disease considered.

A more probable explanation for the hypocholesteremia frequently observed in rheumatic heart disease is the presence of the underlying infectious process. The cholesterol content of the blood is consistently decreased in infectious diseases, especially in the acute febrile disorders⁸ and in the acute stages of syphilis,⁹ leprosy,¹⁰ typhoid¹¹ and tuber-

6 Gorham, F. D., and Myers, V. C. Remarks on the Cholesterol Content of Human Blood, *Arch Int Med* **20** 599 (Oct.) 1917.

7 Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and Van Slyke, D. D. Plasma Lipids of Normal Men at Different Ages, *J Biol Chem* **111** 613, 1935.

8 (a) Bacmeister and Henes, E. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Erkrankungen, *Deutsche med Wchnschr* **39** 544, 1913. (b) Henes, E. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei inneren Erkrankungen, *Deutsches Arch f klin Med* **111** 122, 1913. (c) Wachter, L., and Hueck, W. Chemische und morphologische Untersuchungen über die Bedeutung des Cholesterins im Organismus, *Arch f exper Path u Pharmacol* **74** 416 1913. (d) Kipp, H. A. Variation in the Cholesterol Content of Serum in Pneumonia, *J Biol Chem* **44** 215, 1920. (e) Denis, W. Cholesterol in Human Blood Under Pathological Conditions, *ibid* **29** 93, 1917. (f) Boyd, E. M. The Lipopenia of Fever, *Canad M A J* **32** 500, 1935. (g) Stoesser, A. V., and McQuarrie, I. Influence of Acute Infection and Artificial Fever on the Plasma Lipids, *Am J Dis Child* **49** 658 (March) 1935. (h) Stoesser, A. V. Study of Cholesterol Fractions in Acute Infections of Infants With and Without Eczema, *Proc Soc Exper Biol & Med* **34** 10, 1936.

9 Knudson, A., Ordway, T., and Ferguson, H. Cholesterol and Cholesterol Esters in Blood Showing a Positive Wassermann Reaction, *Proc Soc Exper Biol & Med* **18** 299, 1921. Rosen, I., and Krasnow, F. Blood Cholesterol Findings in Syphilis and Other Skin Diseases. An Accurate Technic for Extracting Blood Cholesterol, *Arch Dermat & Syph* **13** 506 (April) 1926. Feraru, F., and Offenkrantz, F. M. Serum Cholesterol in Syphilis, *Am J Syph, Gonorr & Ven Dis* **21** 267, 1937.

10 Boyd, T. C., and Roy, A. C. Notes on the Cholesterol Content of Indian Blood in Health and Leprosy, *Indian J M Research* **15** 643, 1928.

11 Chauffard, A., Laroche, G., and Grigaut, A. Évolution de la cholestéremie chez les typhiques, *Compt rend Soc de biol* **70** 70, 1911.

culosis¹² In rheumatoid arthritis, a disease presumably infectious in origin, the cholesterol content is also frequently diminished¹³ Kipp^{8a} attempted to explain the low cholesterol value by assuming a greater utilization of this lipid in the body in the presence of infection

Although reports of numerous studies on the cholesterol content of the blood in essential hypertension and arteriosclerosis have been published during the past twenty-five years, the results, even in recent years with improved methods, have not been uniform In 1936 Page, Kirk, and Van Slyke,¹⁴ and Elliot and Nuzum¹⁵ reported that patients with essential hypertension with or without arteriosclerosis did not have an elevated cholesterol level More recently, Davis, Stern and Lesnick¹⁶ found the average cholesterol level to be higher for patients with angina pectoris of atherosclerotic origin than for a group of control subjects Since Saphir and his co-workers¹⁷ have observed that patients with coronary atherosclerosis always manifest generalized arteriosclerosis in the aorta and other vessels of the body, the results of Davis, Stern and Lesnick, as suggested by these writers, indicate that patients with generalized arteriosclerosis manifest a higher average cholesterol value than do normal subjects Our findings in arteriosclerotic heart disease and in hypertensive heart disease with arteriosclerosis also demonstrate that the advent of vascular degeneration in man is frequently accompanied with an elevation of the cholesterol level of the blood

12 Bacmeister and Henes^{8a} Eichelberger, L, and McCluskey, K L Chemical Studies in Tuberculosis I Plasma Proteins, Cholesterol and Corpuscle Volume, Arch Int Med **40** 831 (Dec) 1927 King, S E, and Bruger, M Plasma Cholesterol in Tuberculosis and Amyloid Disease, Ann Int Med **8** 1427, 1935

13 Bruger, M, and Poindexter, C A Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch Int Med **53** 423 (March) 1934 Hartung, E F, and Bruger, M The Cholesterol Content of the Plasma in Arthritis, J Lab & Clin Med **20** 675, 1935

14 Page, I H, Kirk, E, and Van Slyke, D D Plasma Lipids in Essential Hypertension, J Clin Investigation **15** 109, 1936

15 Elliot, A H, and Nuzum, F R Cholesterol Content of Whole Blood in Patients with Arterial Hypertension, Arch Int Med **57** 63 (Jan) 1936

16 Davis, D, Stern, B, and Lesnick, G The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis, Ann Int Med **11** 354, 1937

17 Saphir, O, Priest, W S, Hamburger, W W, and Katz, L N Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am Heart J **10** 762, 1935

CONCLUSIONS

There is a marked difference between the cholesterol content of the plasma of patients with rheumatic heart disease and that of patients with arteriosclerotic or hypertensive heart disease. Patients with rheumatic heart disease frequently demonstrate hypocholesteremia, although for all the patients as a group, the results lack statistical significance when compared with the cholesterol content of the blood of normal subjects. In contrast is the hypercholesteremia often observed for patients with arteriosclerotic heart disease or hypertensive heart disease manifesting some evidence of arteriosclerosis, for these two groups, however, the increase in the plasma cholesterol value is of sufficient magnitude to be statistically significant. For the most part, there is little or no difference between the ratio of ester to free cholesterol in the three types of heart disease studied.

CLINICAL STUDIES OF RESPIRATION

VI EXPIRATORY INFLATION DURING AIR HUNGER AND DYSPNEA PRODUCED BY PHYSICAL EXERTION IN NORMAL SUBJECTS AND IN PATIENTS WITH HEART DISEASE

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Extreme expiratory inflation was apparently of major importance in the production of air hunger and dyspnea in several of our patients with the effort syndrome. These observations suggested that enlargement of the expiratory volume of the chest might be a factor in the production of air hunger and dyspnea in patients with cardiac failure. In a previous study¹ the respirations were stimulated by reducing the oxygen or increasing the carbon dioxide content of the inspired air, both separately and simultaneously, and it was found that patients with cardiac failure were able to tolerate as great alterations of the inspired air as those tolerated by normal subjects. The former group, on the other hand, were unable to perform as much physical exercise as the normal subjects. These observations indicate that the respiratory stimulus produced by physical exertion is different from that produced by alteration of the inspired air. The purpose of the present study was to ascertain the effect of hyperpnea produced by physical exertion on the expiratory volume of the chest of normal subjects and of patients with heart disease.

METHOD

Plethysmograms were obtained by the method previously described². The apparatus was arranged at the beginning of each experiment (fig 1) and was

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1 Greene, J A, and Heeren, R H. Clinical Studies of Respiration. V. Relation of Dyspnea and Air Hunger to Changes of the Expiratory Volume of the Chest, Arch Int Med **57** 100 (Jan) 1936

2 Greene, J A, and Coggeshall, H C. Clinical Studies of Respiration. I. Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man, Arch Int Med **52** 33 (July) 1933

not altered during the period of observation. A control period was continued until the pulse rate and the arterial pressure, which were recorded at one minute intervals throughout the experiment, and the expiratory volume became constant. Physical exertion was obtained by having the subject pedal a stationary bicycle while he reclined in a chair. The duration of exertion varied, but it was continued until definite shortness of breath developed. The same degree of dyspnea was not produced in each instance. The distance traveled, which was measured by an odometer, also varied. Recovery from the exertion was considered complete after the pulse rate and the arterial pressure had reached the previous resting levels and the expiratory volume had become constant. Observations were continued in each experiment for at least ten minutes after recovery. Activity altered the

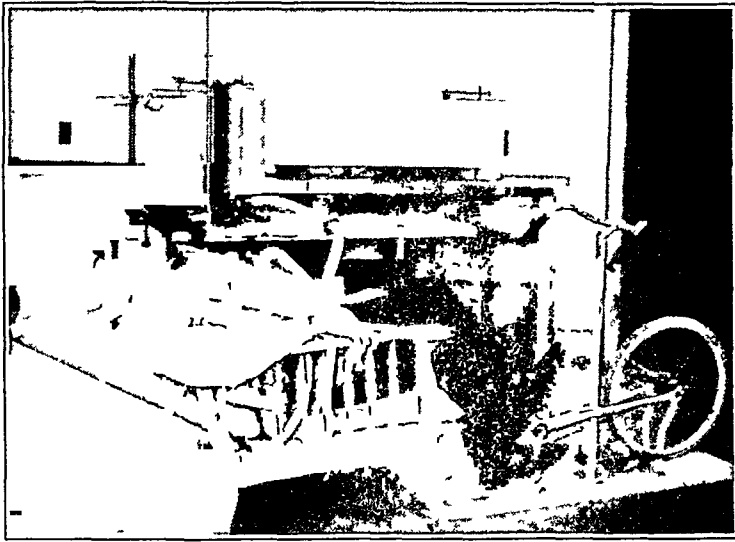


Fig 1—The subject is shown in a reclining position, with the plethysmograph in place, pedaling a bicycle

relation of the subject to the plethysmographic bag, therefore, only records obtained during the period of recovery were studied.

The control group consisted of 12 normal medical students and physicians. Of the 17 patients studied, 3 had arthritis of the spine, 1 aplastic anemia, 1 allergic asthma and pulmonary emphysema and 12 organic heart disease. The last group included 3 without congestive failure and 6 with slight, 1 with moderate and 2 with advanced congestive failure.

RESULTS

The expiratory volume of the chest increased in all instances during hyperpnea produced by physical exertion. A typical example is shown in figure 2.

Three possible sources of error had to be excluded before these results could be accepted. First, the apparatus recorded the complete expirations during hyperpnea, second, muscular relaxation was complete

immediately after the occurrence of exertion, and, third, flexion or extension of the spine did not produce the results. The first possible source of error was excluded because forced expirations during hyperpnea were recorded (fig 3). The second was difficult to eliminate, but

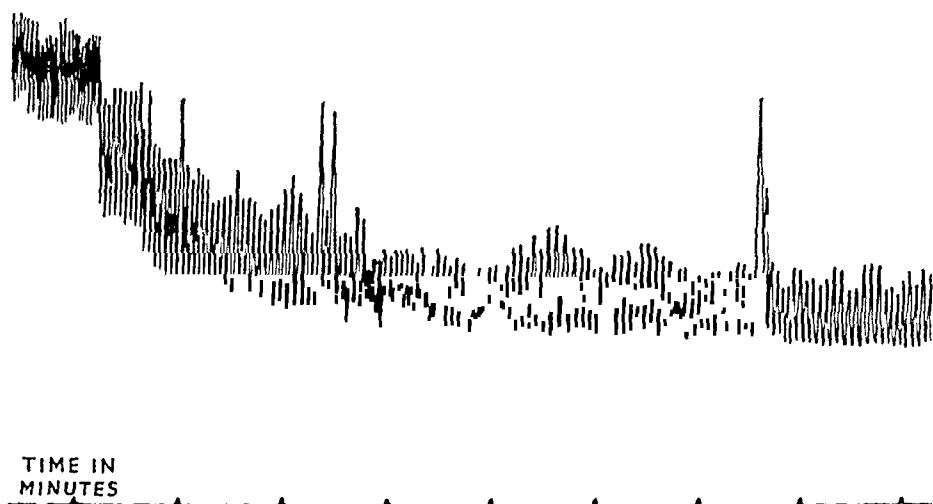


Fig 2—Plethysmogram taken during recovery from physical exertion, showing expiratory deflation

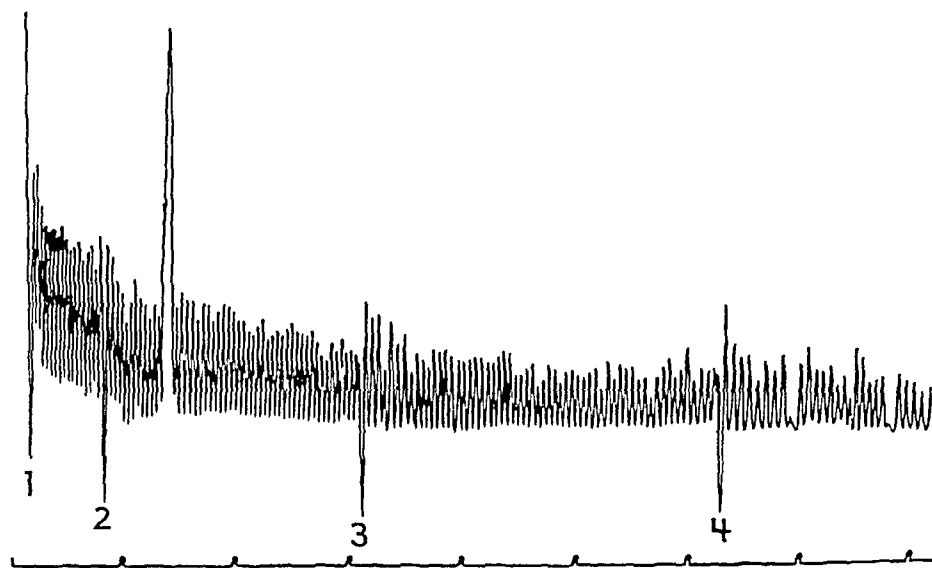


Fig 3—Plethysmogram taken during recovery from physical exertion. Forced expirations are recorded at 1, 2, 3 and 4

each person felt that muscular relaxation was complete as soon as the exertion ended. The third was excluded by the occurrence of alterations in the expiratory volume of the chest of patients with immobility of the spine due to arthritis.

Greater expiratory inflation occurred in patients with heart disease than in normal subjects. As graphically recorded, the inflations averaged 38.9 mm., as compared to 30.1 mm. It will be noted from table 1 that this phase also persisted longer in proportion to the distance recorded on the odometer in patients with cardiac disease.

TABLE 1—*Comparison of the Duration of Expiratory Inflation and the Distance Traveled**

Subjects	Average Distance, Miles	Average Duration of Expiratory Inflation, Minutes
Normal subjects	2.9	6.6
Patients with heart disease	0.6	5.8
Others	0.9	4.9

* The expiratory inflation persisted longer in proportion to the distance traveled in patients with heart disease than in normal subjects.

TABLE 2—*Comparative Data on the Duration of Expiratory Inflation, the Distance Traveled and the Severity of Congestive Heart Failure*

Degree of Heart Failure	Average Distance, Miles	Average Duration of Expiratory Inflation, Minutes
None	0.7	5.7
Slight	0.8	6.0
Moderate	0.4	6.0
Severe	0.2	5.5

* The more severe the congestive heart failure, the longer the expiratory inflation persisted in proportion to the amount of physical exertion.

TABLE 3—*Comparative Data on the Pulse Rate, Arterial Pressure and Duration of Expiratory Inflation*

Subjects	Average Increase of Pulse Rate, Beats per Minute	Average Elevation of Arterial Pressure (Systolic) Mm. of Hg	Average Duration of Expiratory Inflation, Minutes
Normal	58	48	6.6
Patients with heart disease	29	20	5.8
Others	70	26	4.9

* Although there was a greater relative demand placed on the cardiocirculatory system of normal subjects, as shown by the increase in pulse rate and arterial pressure, the duration of the expiratory inflation was proportionately less than that for patients with heart disease.

The duration of altered thoracic volume was less in proportion to the degree of exertion for patients with heart disease without failure than for those with congestive failure (table 2).

The patients exerted themselves less vigorously than did the normal subjects, and a longer time was required to pedal the same distance, consequently, the duration of expiratory inflation was compared to the maximum increase of pulse rate and of arterial pressure. It will be noted from table 3 that the patients with heart disease had relatively less strain on the cardiocirculatory system, yet the expiratory inflation persisted proportionately longer than in the normal subjects. Two normal subjects, not included in the table, showed a persistent elevation of thoracic volume out of proportion to the distance traveled or to the relative strain on the cardiocirculatory system.

COMMENT

The occurrence of expiratory inflation during hyperpnea in all instances after physical exertion indicates that this is a normal response to hyperpnea thus produced. Our findings are in accord with those of Bohr³ and Siebeck,⁴ who observed an increase in the middle position of the chest after physical exertion.

The greater and proportionately longer expiratory inflation observed in our patients with heart disease could be attributed to an abnormal respiratory response to a given amount of physical exertion, as pointed out by Harrison, Harrison, Calhoun and Marsh.⁵

Expiratory enlargement of the chest decreases the effective vital capacity, which is already diminished in cases of cardiac failure, and is undoubtedly a contributory factor in the production of air hunger and dyspnea. In certain patients with effort syndrome, expiratory inflation became so marked that only small expirations were possible, consequently, the respirations became shallow and rapid. Such extreme expiratory enlargement was not observed in any patient with cardiac failure, therefore, it appears that this phenomenon is not as important in the production of air hunger and dyspnea in cases of heart failure as in effort syndrome.

SUMMARY

The expiratory volume of the chest has been studied during hyperpnea produced by physical exertion in normal subjects and in patients

3 Bohr, C. Die funktionellen Aenderungen in der Mittellage und Vitalkapazität der Lungen, *Deutsches Arch f klin Med* **88** 385, 1906-1907.

4 Siebeck, R. Ueber die Beeinflussung der Atemmechanik durch krankhafte Zustände des Respirations-und Kreislaufapparates, *Deutsches Arch f klin Med* **100** 204, 1910.

5 Harrison, T. R., Harrison, W. G., Calhoun, J. A., and Marsh, J. P. Congestive Heart Failure. XVII. The Mechanism of Dyspnea on Exertion, *Arch Int Med* **50** 690 (Nov) 1932.

with heart disease. The increase observed in all instances was of greater degree and proportionately of longer duration in the patients. These results indicate that expiratory inflation per se is not the major factor in the production of air hunger and dyspnea in cases of cardiac failure.

DIRECT MEASUREMENT OF HEIGHT OF THYROID EPITHELIUM

A METHOD OF ASSAY OF THYROTROPIC SUBSTANCE,
CLINICAL APPLICATION

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A convenient, specific and delicate method of assay of the thyrotropic principle of the anterior lobe of the pituitary body is required for physiologic and clinical studies. Various methods have been used. Loeb¹ and his associates, in 1928, described a quantitative method that had been used by them for several years, namely, the determination of the mitotic index. The entire thyroid gland of the test animal, the guinea pig, was cut in serial section and stained with hematoxylin and eosin. The average number of sections obtained for each gland varied between four hundred and fifty and five hundred, mitoses were counted in every tenth section in an exact manner, the number of mitoses thus obtained was multiplied by 10 to obtain the total number of mitoses in the gland. A marked increase in the number of mitoses occurs with thyroid hypertrophy.

Several workers have described the degrees of hyperplastic change resulting from the administration of increasing amounts of thyrotropic substance (Aron,² Loeser³ and Severinghaus⁴). Junkmann and Schoeller⁵ have given a more detailed description and have proposed

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1 Loeb, L, cited by Rabinovitch, J. The Effect of Feeding Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, *Am J Path* **4** 601-611, 1928

2 Aron, M. L'hormone prehypophysaire excito-secretrice de la thyroide. Contribution a l'etude du fonctionnement thyroïdien, *Rev franç d'endocrinol* **8** 472-520, 1930

3 Loeser, A. Die Darstellung thyreotropwirksamer Extrakte aus Hypophysenvorderlappen, *Arch f exper Path u Pharmacol* **166** 693-702, 1932

4 Severinghaus, A E. Cytological Observations on the Secretion in Normal and Activated Thyroids, *Ztschr f Zellforsch u mikr Anat* **19** 653-680, 1933

5 Junkmann, K, and Schoeller, W. Ueber das thyreotrope Hormon des Hypophysenvorderlappens, *Klin Wchnschr* **11** 1176-1177, 1932

a unit of thyrotropic activity in terms of the microscopic picture of hyperplasia Collip⁶ has defined a unit as "the minimum amount administered daily in two injections which will cause a rise of 20 per cent in the metabolism of the hypophysectomized rats by the fourth day" Cuyler, Stimmel and McCullagh⁷ have resorted to determination of the total iodine content of the thyroid gland to measure thyrotropic activity The iodine content decreases with stimulation One unit was considered to be the amount which would decrease the iodine content to half the average normal content The acceleration of the metamorphosis of tadpoles was also used by these authors to quantitate thyrotropic activity Klein⁸ suggested determining the average diameter of a hundred follicles—the follicular index—as a method of representing the degree of colloid storage in the gland Hertz and Oastler⁹ determined the presence of thyrotropic substance without measurement of the amount by the ability of the unknown material to prevent atrophy of the thyroid gland of the rat after hypophysectomy Heyl and Laqueur¹⁰ reviewed the problem of quantitative assay of thyrotropic substance, rejected the indirect methods based on metabolism and also the method based on the weight of the gland and returned to analyses of the visual impression of the hyperplastic changes, which occur chiefly in the center of the gland They defined six stages Recently Aron¹¹ reconsidered the problem and suggested that a unit of thyrotropic activity would be the amount producing a certain increase, for instance, of 5 to 10 in the number of mitoses per microscopic field in the thyroid gland of the guinea pig

This problem was clearly stated in the important contribution by Rowlands and Parkes¹² After considering the preceding methods they resorted to the common procedure of bioassay, namely, study of the

6 Collip, J. B., and Anderson, E. M. The Production of Serum Inhibitory to the Thyrotropic Hormone, *Lancet* **1** 76-78, 1934

7 Cuyler, W. K., Stimmel, B. F., and McCullagh, D. R. Quantitative Studies with Thyrotropic Hormone, *J. Pharmacol. & Exper. Therap.* **58** 286-293, 1936

8 Klein, J. The Correlation of Mineral Metabolism and the Vegetative Nervous System in Thyroid Disease, *Ann. Int. Med.* **8** 798-804, 1935

9 Hertz, S., and Oastler, E. G. Assay of Blood and Urine for Thyrotropic Hormone in Thyrotoxicosis and Myxedema, *Endocrinology* **20** 520-525, 1936

10 Heyl, J. G., and Laqueur, E. Zur quantitativen Bestimmung der thyreotropen Wirkung von Hypophysenvorderlappenpräparaten und die Einheit des thyreotropen Hormons, *Arch. internat. de pharmacodyn. et de therap.* **49** 338-354, 1935

11 Aron, M. Sur le titrage biologique de la thyreostimuline prehypophysaire. Le "seuil des mitoses" dans la thyroïde des cobayes traites, *Compt. rend. Soc. de biol.* **123** 250-253, 1936

12 Rowlands, I. W., and Parkes, A. S. Quantitative Study of the Thyrotropic Activity of Anterior Pituitary Extracts, *Biochem. J.* **282** 1829-1843, 1934

increase in weight of the gland. They were able to show a characteristic curve of increase of weight accompanied by increasing dosage. They defined a unit as the thyrotropic activity contained in an amount of thyrotropic substance which when given daily for five days will cause the thyroid gland of immature guinea pigs to attain a weight of 60 mg (1 e., a doubling of the weight). This weight was determined after fixation of the gland in Bouin's fluid and dehydration to the stage of preparation for sectioning at which 70 per cent alcohol is employed.

No comprehensive study comparing the advantages of these various procedures has been made, but in general it may be assumed that (1) the mitotic index of Loeb, while undoubtedly sensitive, objective and accurate, must be time consuming, (2) the descriptive histologic methods, depending on the visual impression of the individual observer, are not objectively accurate, (3) the metabolic studies of Collip and the thyroid maintenance plan of Hertz require hypophysectomy to render the rat sensitive to thyrotropic substance, Collip's method is indirect, depending on a secondary variable—the sensitivity of the test animal to the thyroid substance produced by its stimulated gland, the Hertz technic requires eight days of maintenance and subsequent comparison and is not quantitative, (4) the only objection to the unit of Rowlands and Parkes is that it may not be small enough (this is not a fundamental criticism of the unit but implies that the method is not a delicate one). For physiologic studies of the guinea pig a method for detecting levels of thyrotropic substance similar to those that are normal for the animal is required to learn the factors normally influencing thyroid physiology. In view of these objections we suggest the following method.

EXPERIMENTAL STUDIES

The actual measurement of the height of the thyroid epithelium may be used to estimate the hyperplasia produced by thyrotropic substance. This procedure is analagous to the Price-Jones¹³ technic for studying red blood cells.

For test animals we use immature female guinea pigs which have been kept on a standard laboratory diet and which weigh from 180 to 225 Gm. The material to be tested is administered in three daily subcutaneous injections. The animal is killed with ether on the fourth day. The thyroid gland is removed on the trachea and fixed in solution of formaldehyde. Paraffin sections are made and stained with hematoxylin and eosin. The section is mounted so that the long axis of the gland is at right angles to the slide, this allows long parallel paths to be followed with the mechanical stage of the microscope. With the oil immersion lens (we use a Leitz echelon micrometer that is calibrated so that one division equals 0.75 microns) the height of the cell of average size in the wall of 200 successive distinct acini is measured. Interacinar cells are neglected.

13 Price-Jones, C. *Red Blood Cell Diameters*, London, Oxford University Press, 1933.

Acini of all diameters are used but only if a distinct lumen is present. These 200 measurements are tabulated, and a graph is made of the frequency curve. The mode, mean, standard deviation and probable error of the mean are determined.

RESULTS

Measurements for untreated animals form curves with modes falling at 3.75 microns (chart 1). The mean heights of the cells calculated

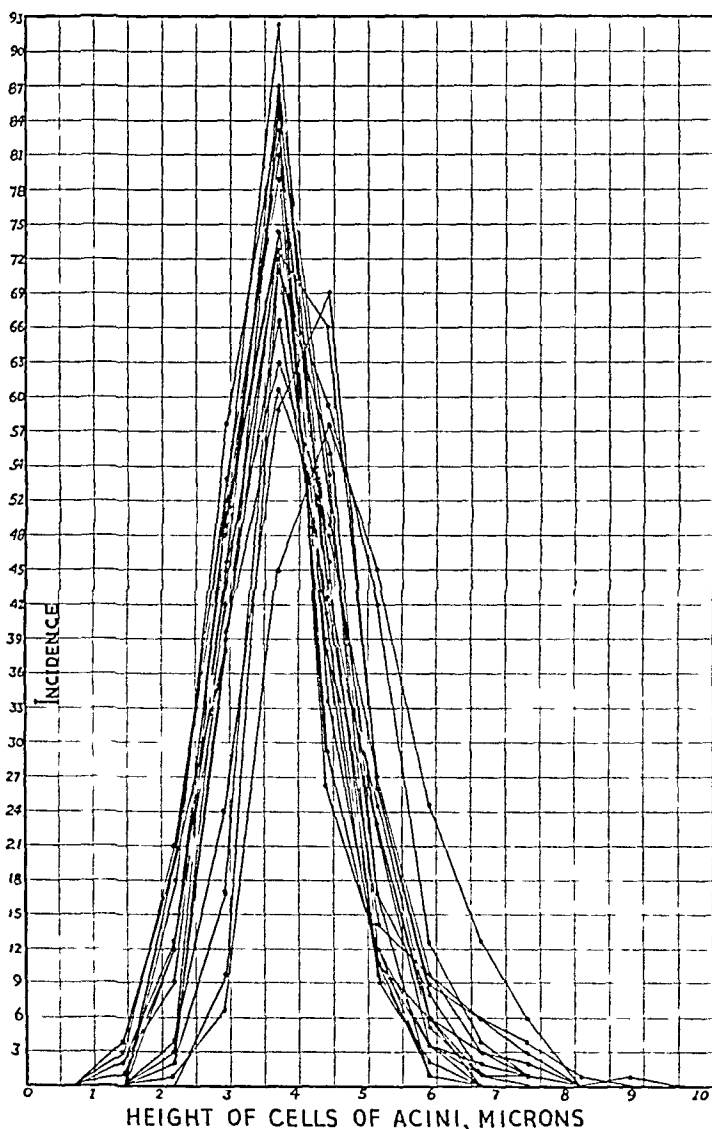


Chart 1—Composite curves for 18 normal untreated guinea pigs. The mean cell heights in the glands ranged from 3.5 to 4.86 microns. The average mean for all the animals was 3.94 microns.

from the curves for 18 control animals measured in July, November, December and February ranged from 3.69 to 3.95 microns. This indicates a rather extraordinary uniformity of control material that is worthy of further investigation. It may be actual, as a result of uniform

diet and breeding, or the variations in hyperplasia apparent to other observers in control animals may not affect enough of the mature acini to shift the curve. Since the condition of this control material is fundamental for the method as it is now arranged, a more detailed analysis of control animals is in progress.

Serial sections cut from the thyroid gland of a control animal and that of an animal treated with thyrotropic substance were measured by the same observer (chart 2). The modes of the five curves from the five successive serial sections of the gland of the control animal were all at 3.75 microns. The mean heights of the cells ranged from 3.6 to 3.98 microns. The modes of five curves from similar sections of the gland of the treated animals were double, at 4.5 and 6 microns. The mean heights of the cells ranged from 6.06 to 6.24 microns. Thus, there was a similar degree of variation in the serial sections and in the control series. The difference in the control glands was 3.95—3.69

Data on Treatment with a Preparation of the Anterior Lobe of the Hypophysis

Experiment No.	Dose, Cc	No. of Glands Counted	Modes, Microns	Range of Means, Microns	Average of Means, Microns
1	Controls	18	3.75	3.59-4.1	3.77 \pm 0.015
2	0.0025	12	4.5	4.5-4.8	4.65 \pm 0.018
3	0.0050	8	4.5-6	4.9-5.6	5.25 \pm 0.02
4	0.0100	5	4.5-6	5.5-6	5.71 \pm 0.029
5	0.0200	5	5.25-6.75	6.1-6.4	6.14 \pm 0.028

or 0.26 microns, the differences in the serial sections were 3.98—3.60 or 0.38 microns, and 6.24—6.06, or 0.18 microns.

A preparation of the anterior lobe of the bovine hypophysis¹⁴ containing thyrotropic principle was administered subcutaneously for three days. After treatment with three daily doses of 0.0025 cc each, the curves had a mode at 4.5 microns (chart 3A). The mean heights of the cells of 8 such animals ranged from 4.5 to 4.8 microns. After treatment with three daily doses of 0.005 cc each, the mode for 8 animals was 4.5 microns (chart 3B), but the mean heights ranged from 4.9 to 5.6 microns. After 0.01 cc doses the curves were bimodal, at 4.5 and 6 microns (chart 4A), the mean heights for 5 animals ranged from 5.5 to 6 microns. After 0.02 cc the curves also were bimodal, at 5.25 and 6.75 microns (chart 4B), and the mean heights for 5 animals ranged from 6.1 to 6.4 microns. These data are shown in the accompanying table.

Still greater shifts of the curve to the right was evident with 0.05 and 0.1 cc doses. The general rule seems to be established that there is an increasing shift to the right with increasing doses. This is illustrated in a composite curve (chart 5).

14. The preparation used was antuitrin—T, supplied by Parke, Davis & Co.

CLINICAL STUDIES

The present clinical report on the urinary assay of thyrotropic substance is presented merely as an indication of the direction the study is taking. Extracts from larger quantities of urine it is thought, will bring out the same clinical relations more clearly.

Fifty cubic centimeters of urine collected early in the morning was chilled and filtered, mixed with 450 cc of acetone and allowed to stand for twenty-four hours. The supernatant fluid was siphoned off, and the residue was centrifuged. The precipitate was washed twice with absolute alcohol and twice with anhydrous ether. Ten cubic centimeters of water was then stirred with the precipitate and

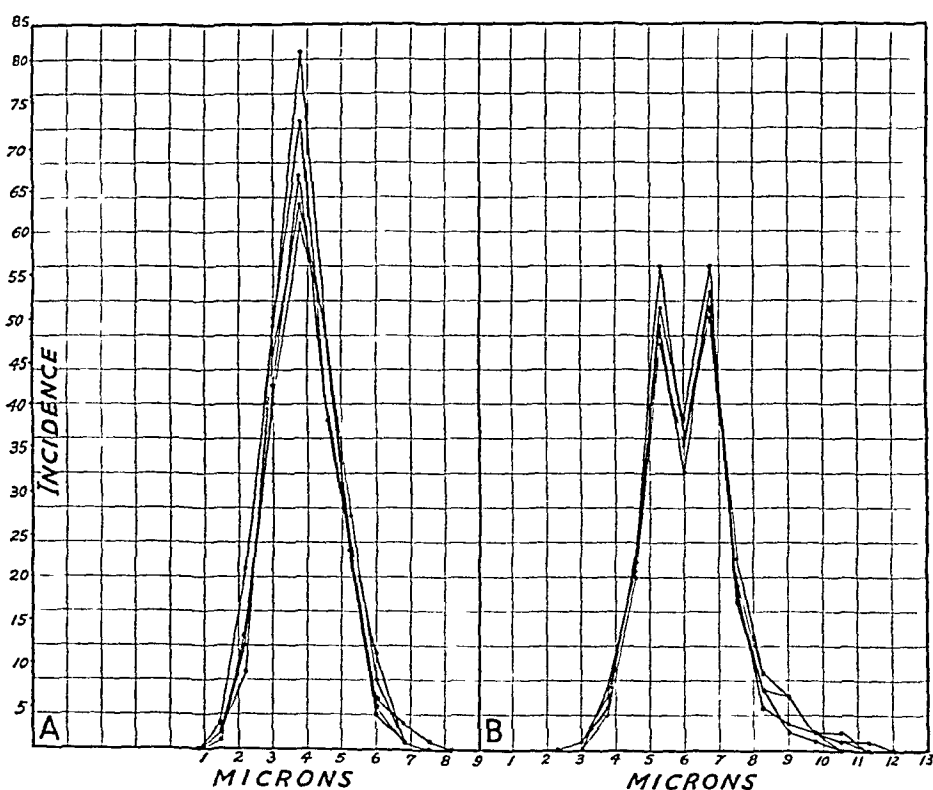


Chart 2—*A*, frequency curves for five successive serial sections from the thyroid gland of an untreated guinea pig. The mode was 3.75 microns and the mean 3.79 microns. *B*, frequency curves for five successive serial sections from the thyroid gland of a guinea pig treated with three daily injections (0.02 cc each) of a preparation of the anterior lobe of the hypophysis. The curves were bimodal, at 4.5 and 6.15 microns. The mean was 6.15 microns.

this was allowed to stand for two or three hours and then centrifuged. The supernatant aqueous solution was given by subcutaneous injection in divided doses during three days to an immature female guinea pig weighing approximately 200 Gm. Whenever possible duplicate studies were made.

Such material from 21 young men and women, apparently normal whose basal metabolic rates ranged from -9 to $+11$ per cent (Aub-

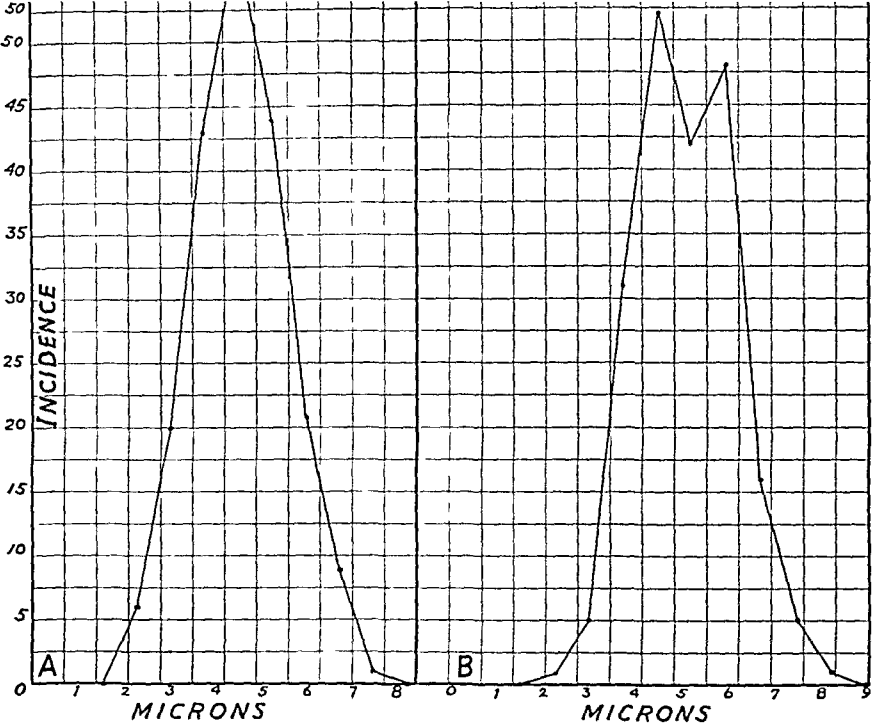


Chart 3—*A*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.0025 cc each of a preparation of the anterior lobe of the hypophysis. The mode was 4.5 microns and the mean cell height 4.57 microns. *B*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.005 cc each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 5.12 microns.

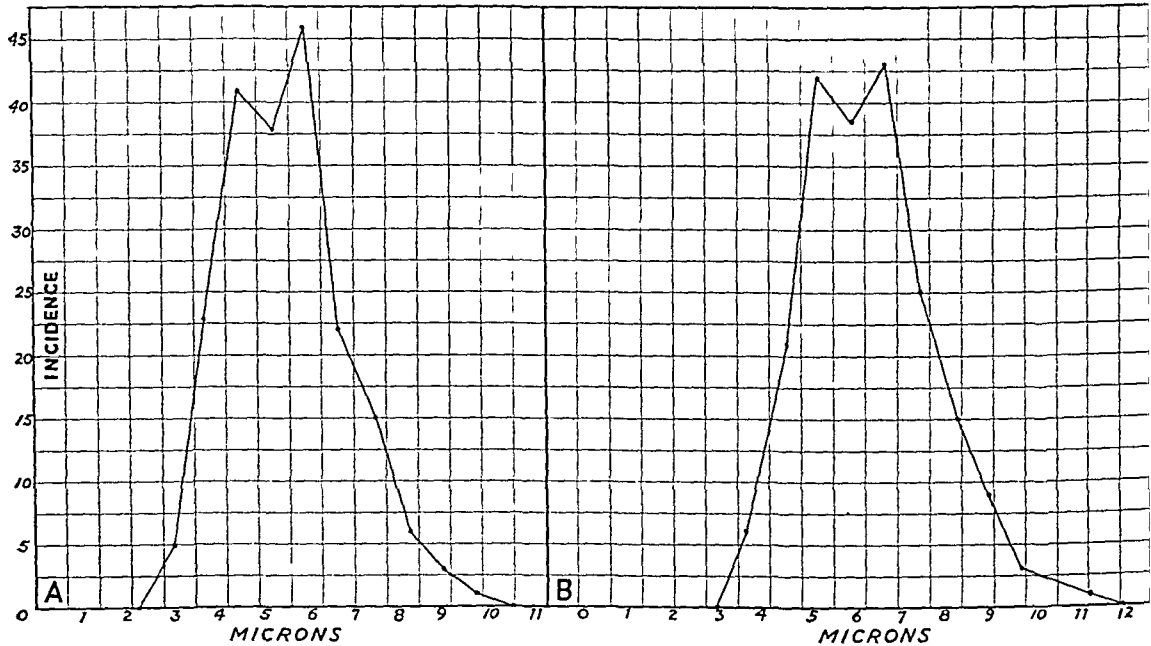


Chart 4—*A*, curve for the thyroid gland of guinea pig which received three daily doses of 0.01 cc each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 5.54 microns. *B*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.02 cc each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 6.36 microns.

Du Bois) produced a slight but definite shift to the right of the control curve (chart 6). The mean heights of the cells ranged from 3.49 ± 0.038 to 5.04 ± 0.042 microns with an average of 4.12 microns.

The difference between the average mean height of the cells of the thyroid glands of the control guinea pigs and that of the guinea

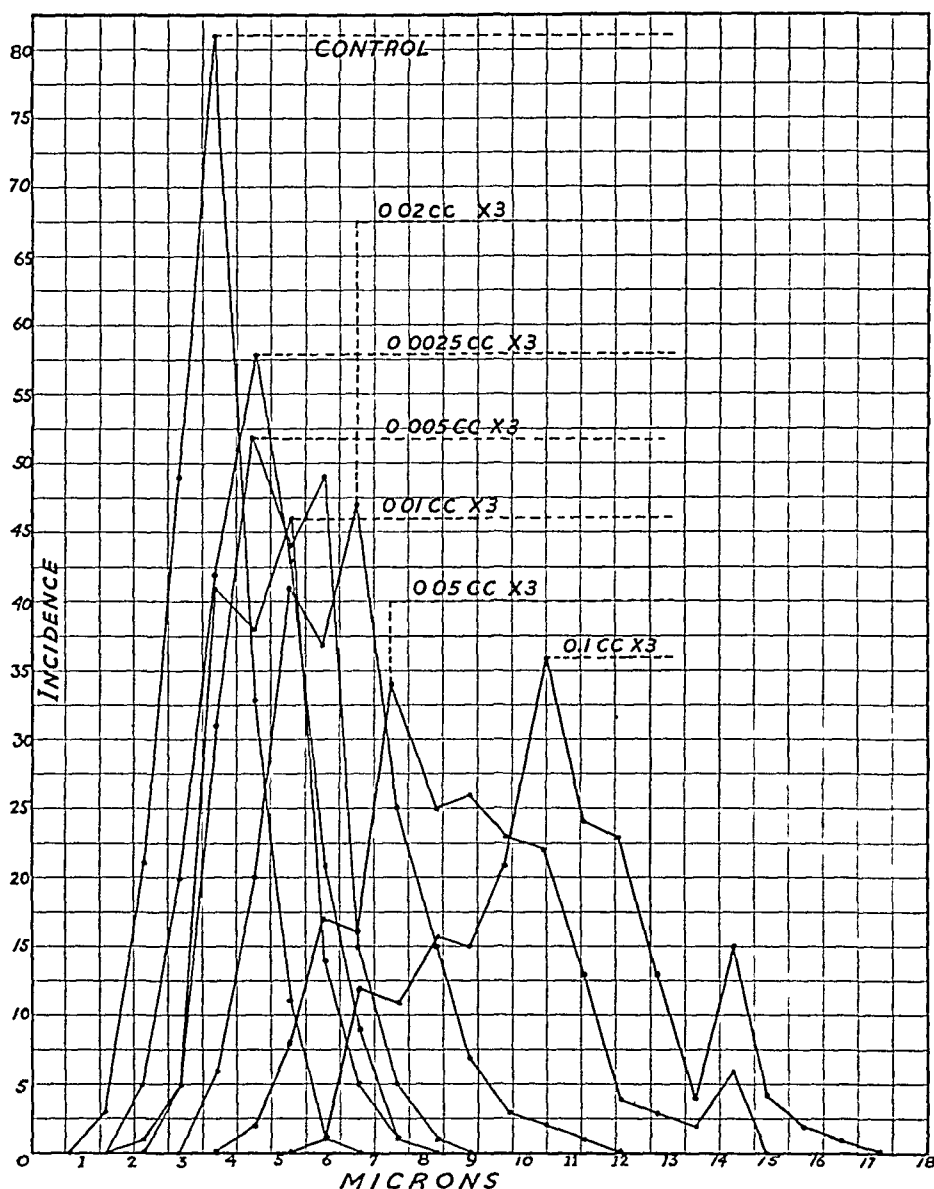


Chart 5—A composite picture of the curves obtained with increasing doses. Note the shift to the right produced by increasing the dosage.

pigs treated with extract of urine from normal persons, e. g., 4.39 ± 0.029 to 3.77 ± 0.015 microns, was great enough to be of statistical significance as compared with the probable error in the measurements of the cells of the control glands (0.015 microns).

Such material from a group of older men and women who were not myxedematous but whose basal metabolic rates ranged from -34 to -17 per cent and who showed values for blood cholesterol ranging from 220 to 305 mg per hundred cubic centimeters produced a further shift to the right in the curve (chart 7). The mean heights of the cells ranged from 3.93 ± 0.028 to 5.92 ± 0.04 microns with an average mean of 4.7 microns.

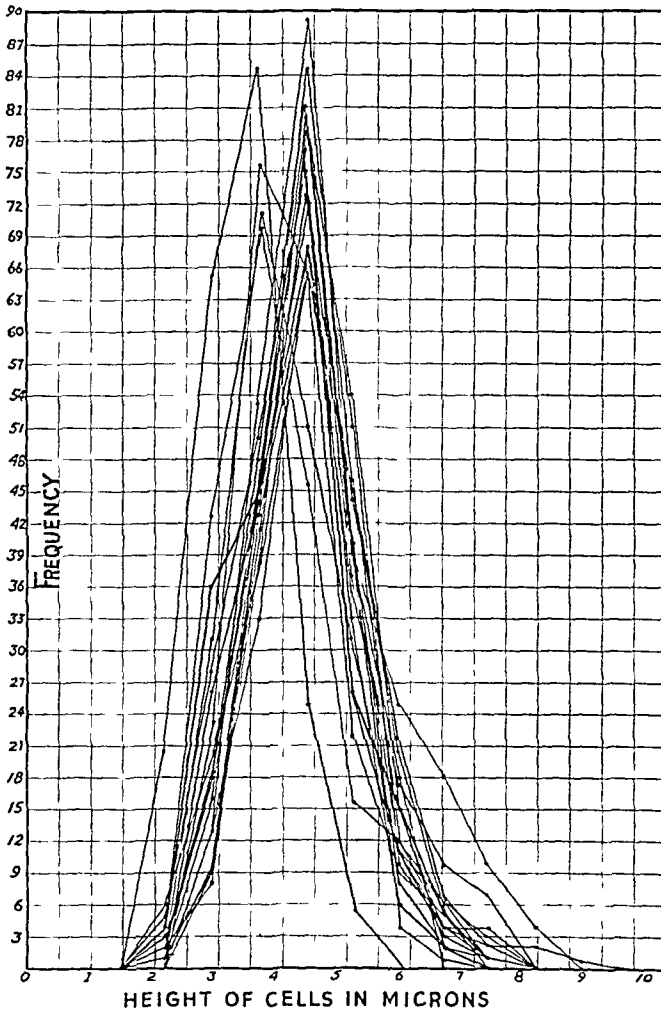


Chart 6—A composite graph of the twenty-one curves for guinea pigs which were given injections of extract of urine from 21 normal persons whose basal metabolic rates ranged from -9 to $+11$ per cent. The mean cell heights ranged from 3.84 to 5.04 microns. The average was 4.4 microns.

Such material from 3 men who had had total thyroidectomy for heart disease, who had not received thyroid therapy but who were not completely myxedematous and whose basal metabolic rates ranged from -31 to -2 per cent produced still greater shift to the right

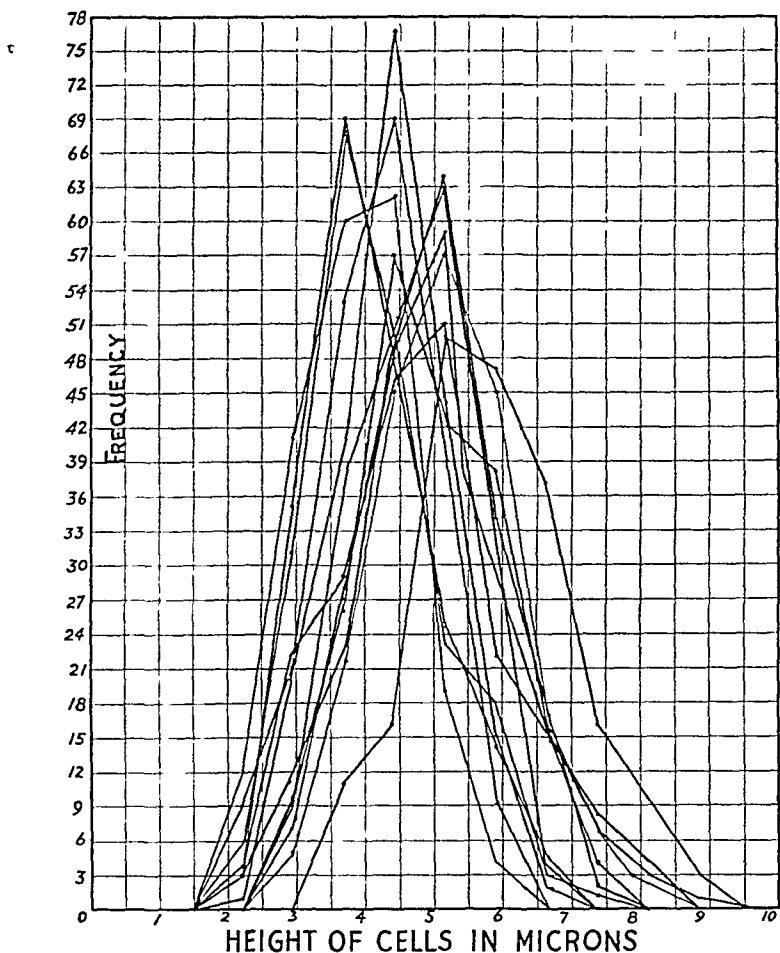


Chart 7—A composite graph of the sixteen curves for guinea pigs which were given injections of extract of urine from 8 patients with low basal metabolic rates, ranging from -16 to -34 per cent, but without clinical signs of myxedema. The mean cell heights ranged from 3.93 microns (controls) to 5.92 microns.

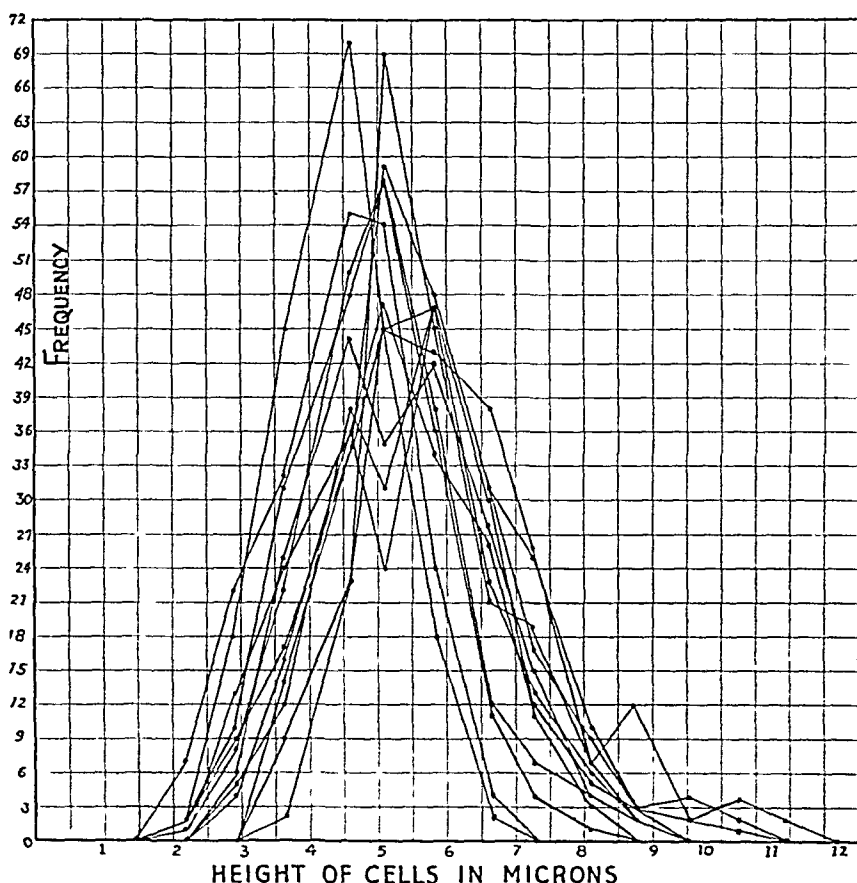


Chart 8—A composite graph of the twelve curves for guinea pigs which were given injections of extract of urine from 3 patients after total thyroidectomy. The mean cell heights ranged from 4.5 to 6.34 microns, with an average of 5.49 microns.

(chart 8) The mean heights of the cells ranged from 4.5 ± 0.029 to 6.34 ± 0.05 microns with an average mean of 5.4 microns

Such material from 14 patients with hyperthyroidism, whose basal metabolic rates ranged from +8 to +90 per cent, produced no shift

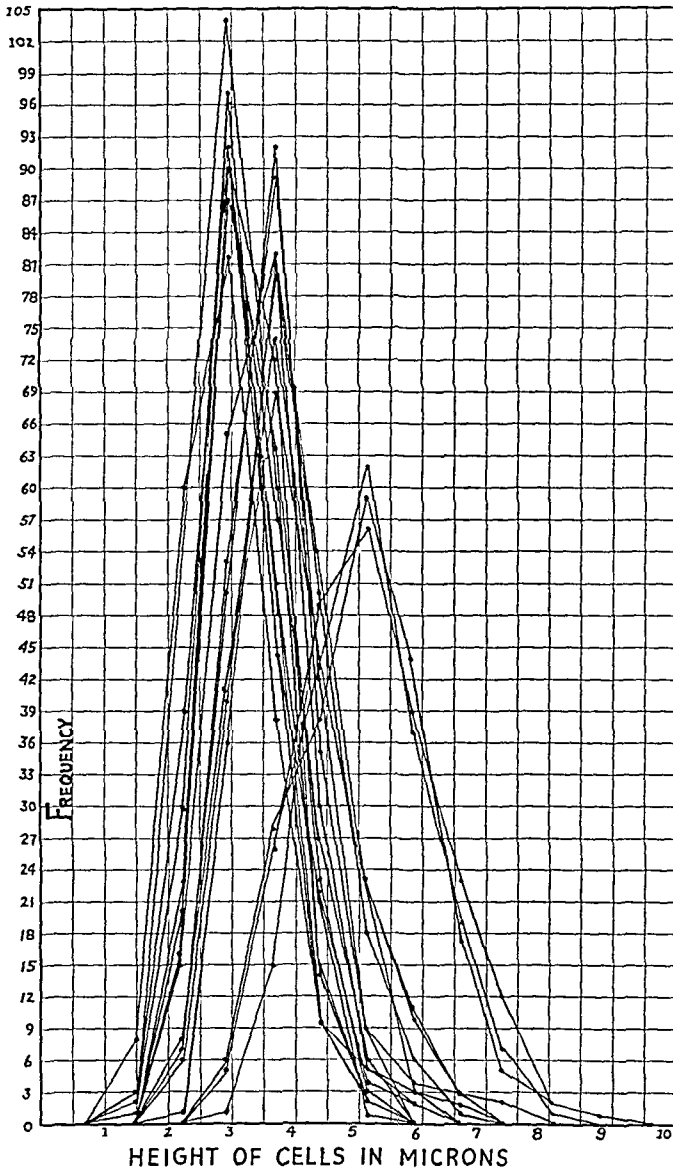


Chart 9—A composite graph of the twenty-nine curves for guinea pigs which received injections of extract of the urine of 14 patients with hyperthyroidism, the basal metabolic rates ranging from +8 to +90 per cent. The mean cell heights ranged from 2.96 to 5.44 microns, with an average of 3.53 microns

in the curve to the right with 2 exceptions (chart 9). Four of these patients who showed negative results of assays for thyrotropic substance in the urine had exophthalmos. The mean heights of the cells

ranged from 2.96 ± 0.02 to 5.44 ± 0.03 microns, with an average mean of 3.53 microns

The possibility that an excess of iodine in the urine of patients with hyperthyroidism would obliterate the effect of any thyrotropic substance present is not completely contradicted, but the addition of 50

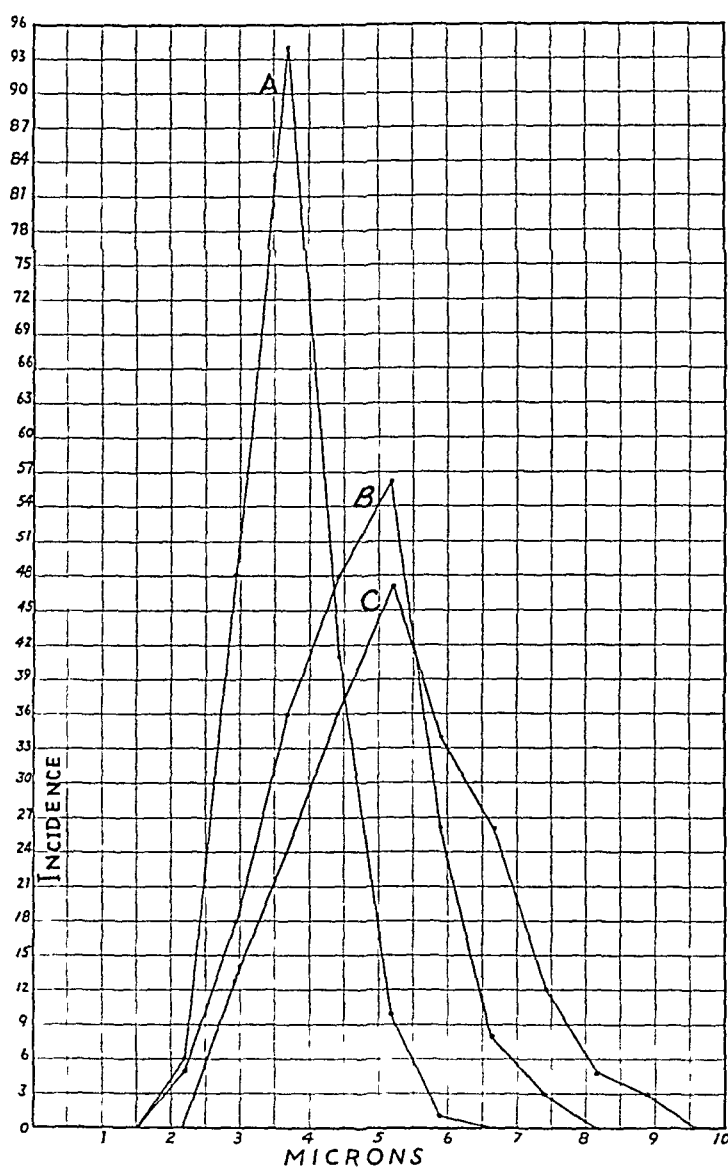


Chart 10—Curves for guinea pigs which received injections of extract of urine from a patient after total thyroidectomy *A*, the urine was heated in order to destroy the thyrotropic substance *B*, 50 micrograms of iodine was added (physiologic in hyperthyroidism) *C*, the usual treatment of the urine was employed

micrograms of iodine to the 50 cc sample of urine from a patient with hypothyroidism following total thyroidectomy did not obliterate that effect (chart 10) This amount of iodine is the aliquot calculated from

the excess of physiologic iodine known to be excreted in hyperthyroidism¹⁵ Heating a specimen from this patient did prevent the effect, since thyrotropic substance is destroyed by heat (chart 10)

SUMMARY AND CONCLUSIONS

The increased height of the acinar epithelium of the guinea pig thyroid induced by thyrotropic substance may be found by direct micrometer measurements, and the hyperplasia throughout the gland may be represented by a frequency curve derived from these measurements

Increasing doses of a solution containing thyrotropic substance produce increasing shifts of such curves to the right

The extract of 50 cc of urine of normal persons produces a slight shift to the right

An extract of 50 cc of urine of nonmyxedematous persons with a low basal metabolic rate may or may not produce a greater effect

The extract of 50 cc of urine of men totally thyroidectomized for heart disease produced a still greater effect

The extract of 50 cc of urine of men and women with hyperthyroidism, with or without exophthalmos, produced no effect except in 2 cases (the occurrence of these exceptions cannot be explained)

15 Curtis, G M Iodine Relationships of Thyroid Disease, Surg, Gynec & Obst **62** 365-371, 1936

THE EXTERNAL SECRETORY FUNCTION OF THE HUMAN PANCREAS

PHYSIOLOGIC OBSERVATIONS

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The earliest basic knowledge of the physiology of the external function of the pancreas came largely as a result of the pioneer studies of two eminent experimental physiologists, Claude Bernard¹ and Ivan Pavlov². The former, in 1856, showed that pancreatic juice is highly essential to digestion, the latter, in 1902, demonstrated the existence of pancreatic enzymes. In the same year Bayliss and Starling³ investigated the factors concerned in the secretory stimulus of the pancreas and assigned the important role to a humoral mechanism which they named secretin.

Many valuable contributions to the physiology of the pancreas have been made during the past thirty years and McClure⁴ in a recent paper has enumerated as follows the important physiologic facts which are now firmly established: 1 Stimulation of the external secretion of the pancreas is of humoral origin, but the exact mechanism remains undetermined. 2 The ingestion of food is followed by secretion of pancreatic juice. 3 The external secretion of the pancreas plays an essential role in digestion. To these facts should perhaps be added the

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Based on material presented in lantern slides by Dr. J. M. McCaughan, at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1937.

1 Bernard, C. *Memoire sur le pancreas et sur le rôle du suc pancréatique dans les phénomènes digestifs, particulièrement dans la digestion des matières grasses neutres*, Paris, J. B. Baillière, 1856.

2 Pavlov, Ivan. *The Work of the Digestive Glands*, translated by W. H. Thompson, London, C. G. Griffin & Co. 1902.

3 Bayliss, W. M., and Starling, E. H. *The Mechanism of Pancreatic Secretion*, *J. Physiol.* **28** 325-353, 1902.

4 McClure, Charles W. *Observations on the Physiology and Pathologic Physiology of External Pancreatic Functions*. *Rev. Gastroenterol.* **3** 1-26, 1936.

observations of Elman and McCaughan⁵ on the rapidly fatal effect in experimental animals of the complete loss of pancreatic juice by total drainage through a fistula

The greater part of the information regarding the external function of the pancreas has been derived either from experiments conducted on lower animals or by indirect experiments on human beings in which the pancreatic juice mixed with other intestinal secretions is obtained for study ordinarily by means of the Rehfuess tube. Considerable interest attaches therefore to reports of clinical experiments performed directly on man. Such observations are possible in cases of pancreatic fistula, and physiologic data of immense value have been accumulated in this manner. The literature contains a great number of case reports dealing with pancreatic fistula, but emphasis is largely given to discussions of the varied pathogenesis and of technical methods of securing closure. Fortunately in a small number of the cases, however, careful chemical and physiologic investigations have been made, with the result that knowledge of human pancreatic physiology has been enriched.

REPORT OF A CASE

The patient, a man aged 49, was admitted to the Firmin Desloge Hospital on Jan 15, 1936, for surgical closure of a pancreatic fistula which had followed a Billroth II type of gastric resection performed elsewhere. The patient stated that the fistula had been draining for more than nine months. The Wohlgemuth antidiabetic treatment had been instituted during this time in an endeavor to bring about healing of the fistula, but the result was unsatisfactory.

On physical examination the patient appeared markedly undernourished. There were a few coarse rales in the left upper portion of the chest posteriorly, but otherwise the thorax was normal. There was an old median operative scar in the upper part of the abdomen, and about 4 cm below the xiphoid process was a tiny cutaneous opening which barely admitted the tip of a small probe. The surrounding skin appeared normal. A clear watery fluid was flowing profusely from this opening, and a sample was collected for identification and study. The systolic blood pressure was 125 mm of mercury and the diastolic pressure 94 mm. On laboratory examination the urine was normal except for an occasional leukocyte and erythrocyte. The blood count showed 7,900 leukocytes and 3,940,000 erythrocytes. The hemoglobin value was 13 Gm. A differential count was normal. The clotting time and bleeding time were both normal, as was the clot retraction time. The sugar, nonprotein-nitrogen, carbon dioxide and chloride values for the blood were within normal limits. A sugar tolerance test by the Shaffer-Hartmann method gave a curve within the normal zone. The Wassermann and Kahn tests of the blood gave negative reactions. Examination of the sputum revealed no abnormality. Gastric analysis showed normal free and combined acids. Roentgenograms of the chest were essentially normal. Fluoroscopic examination of the upper portion of the gastro-intestinal tract showed that the esophagus was normal, the stomach had been resected at its distal third and a gastro-enterostomy

5 Elman, Robert, and McCaughan, John M. On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, *J Exper Med* 45 561-570, 1927

stoma had been made 2 inches (5 cm) proximal to the blind end. The barium sulfate passed freely through the stoma.

On February 1 the fistula was implanted into the anterior wall of the stomach by a method reported elsewhere. The patient made a satisfactory recovery and was discharged from the hospital on March 15. Twelve months after the operation he reported that he had remained entirely well.

Experimental Procedure—Physiologic studies were made previous to operation, and the response to various excitatory and inhibitory drugs and foodstuffs was recorded. A small glass funnel was first applied to the skin about the opening of the fistula and was held there with adhesive tape. The patient was placed in the prone position on two tables set end to end in such a manner that the secretion could drop between the tables and into the recording and collecting apparatus. At least two hours was permitted to elapse after a meal before the beginning of the experiment. Samples of the secretion were collected at regular intervals, usually every fifteen minutes. The total alkali in each specimen was titrated with tenth-normal hydrochloric acid, and the rate of flow was measured before and after each experiment.

Experimental Results—In order not to submit the patient to the risk of possible infection through introduction of a cannula into the fistula, the total volume of pancreatic juice discharged in twenty-four hours was estimated by calculations based on the average rate of flow noted during numerous experiments. An approximate estimate of 600 cc per diem was obtained. The amount of secretion was found to be least during fasting and greatest after meals.

Comment—In the twenty-seven investigations reviewed by us regarding the amount of pancreatic juice discharged from a pancreatic fistula, the least amount (30 to 40 cc) was recorded by Graf⁶ and the largest (1,186 cc) by Snyder and Lium.⁷

Ellinger and Cohn⁸ were among the first (1905) to note that the secretion of pancreatic juice in human beings is continuous. Since then this observation has been confirmed many times.⁹

6 Graf, P. Zur Kasuistik der traumatischen Pankreaszysten, München med Wchnschr **57** 2529-2531, 1910.

7 Snyder, William H., and Lium, Rolf. Pancreatic Fistula, Surg., Gynec. & Obst. **62** 57-64, 1936.

8 Ellinger, A., and Cohn, M. Beiträge zur Kenntnis der Pankreassekretion beim Menschen, Ztschr. f. physiol. Chem. **45** 28-37, 1905.

9 (a) Babkin, B. P. Die äussere Sekretion der Verdauungsdrüsen, ed. 2, Berlin, Julius Springer, 1928, pp. 452-629. (b) von Friedrich, Ladislaus. Ein Fall von Pankreasfistel, Klin. Wchnschr. **1** 1658, 1922. (c) Glaessner, K., and Popper, H. Zur Physiologie und Pathologie des Pankreasfistel-Sekretes, Deutsches Arch. f. klin. Med. **94** 46-60, 1908. (d) Holsti, O. Beiträge zur Kenntnis der Pankreassekretion beim Menschen, *ibid.* **111** 48-92, 1913. (e) Kahn, J., and Klein, H. M. Human Pancreatic Secretion Studies from a Case of Pancreatic Cyst with Fistula, Am. J. M. Sc. **184** 503-511, 1932. (f) Kogut, B., Matzner, J., and Sobel, A. E. A Study of External Pancreatic Secretion in Man, J. Clin. Investigation **15** 393-396, 1936. (g) Rivier, P. Contribution à l'étude de la fonction pancréatique chez l'homme, cas de rupture traumatique du pancréas, Compt. rend. Soc. de biol. **97** 699-670, 1927. (h) Weaver, M. M., Luckhardt, A. B., and Koch, F. C. Preparation of a Potent Vaso Dilatin-Free Pancreatic Secretin, J. A. M. A. **87** 640-645 (Aug. 28) 1926.

CHEMICAL COMPOSITION OF HUMAN PANCREATIC JUICE

The chemical composition of human pancreatic juice has been so adequately studied by others, notably Ellinger and Cohn,⁸ Friedrich,^{9b} Glaessner,¹⁰ Glaessner and Popper,^{9c} Holsti,^{9d} Kahn and Klein,^{9e} Schumm¹¹ and Villard and Labry,¹² that we felt little would be accomplished by repetition of their work. Our investigation, therefore, was limited to relatively few determinations, and these were carried out mainly for the purpose of identification. The fluid was watery, at times it was clear and at other times opalescent. Sometimes a slightly yellow tinge was noticeable. The specific gravity of a single specimen was 1.005, and the p_H was 8.65. The reaction was alkaline to methyl red, and the titratable alkalinity was equivalent to 65 cc. of tenth-normal alkali to 100 cc. of the fluid. A trace of protein was shown to tests with acetic acid and ferrocyanide. Lipase, amylase and inactive trypsin were present.

EFFECT OF HORMONES, DRUGS AND FOODSTUFFS ON THE RATE OF SECRETION AND ON THE TOTAL BASE

The curves of secretion showed considerable fluctuation, and our conclusions have been based on the difference between the average rate before and the average rate after the administration of the substance under investigation. In some curves the initial rate appeared greatest. The explanation is that the fistula tract acted as a reservoir while the subject was in the recumbent position, and several cubic centimeters of pancreatic juice necessarily accumulated. When the patient was turned face down, the tract emptied rapidly and gave an apparent but false picture of active secretion. We therefore waited until the rate became fairly constant before beginning the experiments.

1 *Secretin*.—A protein-free secretin was prepared according to the method of Weaver, Luckhardt and Koch^{9h} and was sterilized before being used. This preparation was tested for possible toxic action on both dogs and guinea pigs. The effect of the secretin preparation on an unanesthetized dog with a pancreatic fistula is shown in chart 1.

The first experiment (chart 1), in which 2 cc. of secretin was injected intramuscularly in our subject, showed a marked rise in total base which lasted for between fifteen and thirty minutes and an increase in the rate

10 Glaessner, K. Ueber menschliches Pankreassekret, *Ztschr. f. physiol. Chem.* **40** 465-479, 1903-1904.

11 Schumm, O. Ueber menschliches Pancreassekret, *Ztschr. f. physiol. Chem.* **36** 292-332, 1902.

12 Villard, M., and Labry, R. Pseudo-kyste du pancreas. Fistule pancreatique post-operative, remarques physiologiques et therapeutiques, *Lyon med.* **142** 424-428, 1928.

of flow from an average of 3 drops a minute to an average of 7 drops a minute. After a second injection of 3 cc of secretin fifteen minutes later there was no further response. A second experiment with secretin (chart 7) in which the total base was not determined showed a rise in the rate of secretion from an average of 6.4 drops to an average of 10 drops a minute after injection of 2.5 cc of secretin intramuscularly, but no further rise occurred after two subsequent injections of 2.5 cc.

Comment. The effect of our preparation of secretin on the dog was similar to that observed by other investigators.¹³ Secretin when administered to the human subject produced a definite increase in the rate of secretion. Snyder and Lum reported inconclusive results after an injection of 6 mg of secretin. The flow of pancreatic juice has been much more pronounced and constant after the administration of secretin in animals than it has been in human beings. McClure has suggested that

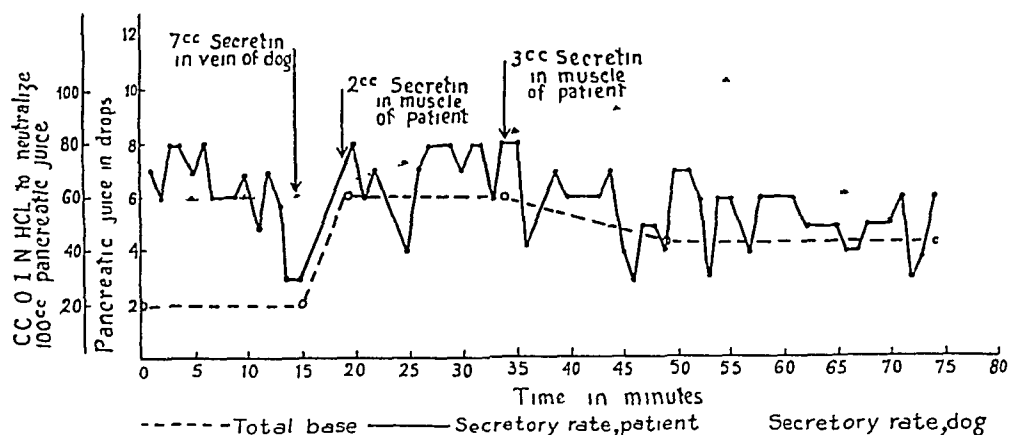


Chart 1—The effect of secretin on the external secretory function of the human pancreas (secretory curve of a control animal is also shown)

this result can be explained by the marked habitual differences in the diets of dogs and of human beings, that of the latter being more complex.

2 Water.—This experiment was begun four hours after the last meal. The flow was observed for thirty minutes and was found to average 3 drops a minute. At the end of this period the patient drank 150 cc of water (chart 7). An increase in flow began almost immediately and averaged about 7 drops a minute for ten minutes.

Comment. Snyder and Lum similarly obtained an immediate and striking response after the administration of water by mouth. Ivy^{13c} has shown that when a given quantity of water is taken by mouth and

13 (a) Farrell, J. I., and Ivy, A. C. Contributions to the Physiology of the Pancreas. II. The Proof of a Humoral Mechanism of External Pancreatic Secretion, *Am J Physiol* **78** 325-338, 1926. (b) Graf.⁶ (c) Ivy, A. C. Studies in Water Drinking, *Am J Physiol* **46** 420-442, 1918. (d) McClure.⁴

then immediately aspirated from the stomach by tube and measured, a small portion (5 to 10 cc) of the water is lost almost instantly into the duodenum along with the gastric secretagogues. This may be the cause of the increased flow after the drinking of water.

3 *Beef Broth*—Fifty cubic centimeters of beef broth was given by duodenal tube. A slight rise in rate of secretion and a fall in total base from 100 to 68 took place (chart 7).

Comment. The results of animal experiments with pure foodstuffs with regard to the amount of pancreatic juice secreted and the concentration of enzymes are not always applicable directly to man. Most observers, however, hold that the flow is greatest after the taking of carbohydrate, less after the taking of protein and least after the taking

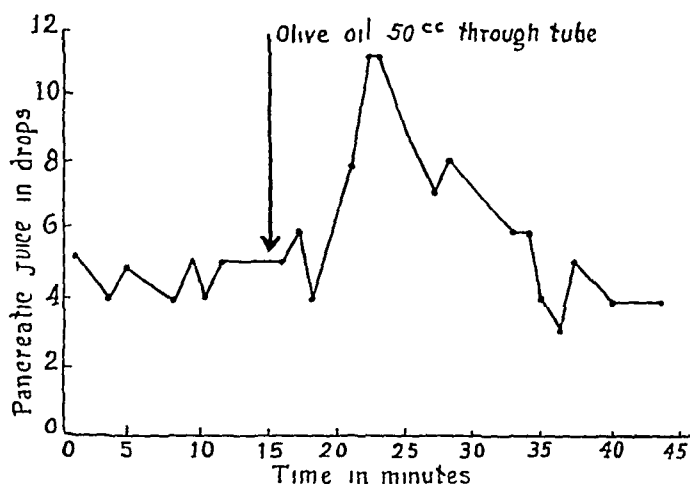


Chart 2—The effect of olive oil on the external secretory function of the human pancreas

of fat. In secretion curves after the administration of protein Holsti noted an initial rise, followed by a fall to zero until the middle of the second hour, and then a second rise which reached a maximum in either the third or the fourth hour.

4 *Olive Oil*—Fifty cubic centimeters of olive oil was given by tube. The rate began to increase almost immediately, reaching 11 drops a minute in seven minutes and gradually falling to 4 drops a minute twenty-five minutes later. The total base was not determined in this experiment (chart 2).

Comment. Ivy^{18c} applied olive oil to the jejunal fistula of a dog and observed no increase in rate of secretion in a transplant of the pancreas in which the normal blood and nerve supply had been completely excluded. Most observers record the largest volume of pancreatic secre-

tion after a carbohydrate meal and the least amount after fatty foods, but Mocquot, Joltrain and Laudat¹⁴ obtained the least response after a meal of meat

5 *Dextrose*—Fifty cubic centimeters of 50 per cent dextrose was introduced into the tube. An immediate rise from about 7 drops a minute to 13 drops a minute was noted, but after about ten minutes the rate fell from a mean level of 10 drops a minute to 5.5 drops a minute, and this level was maintained for twenty minutes, after which the experiment was terminated. The total base fell from 65 to 44 after the introduction of dextrose (chart 3)

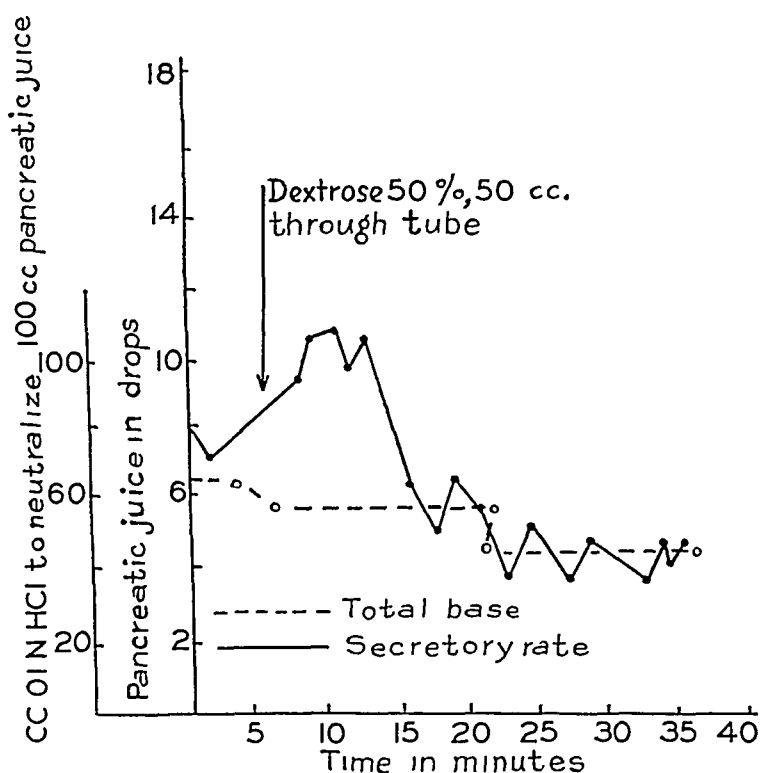


Chart 3—The effect of dextrose on the external secretory function of the human pancreas

Comment Snyder and Lium observed a slow response to dextrose and attributed it to a delayed emptying time of the stomach caused by the hypertonic solution. This explanation may not hold in our case because of the fact that the pyloric sphincter had been resected along with the antrum of the stomach. Holsti¹⁴ and Wohlgemuth¹⁵ obtained a rise after the administration of pure carbohydrate.

14 Mocquot, Joltrain, E., and Laudat. Abces du pancreas d'origine colibacillaire, fistule avec écoulement de suc pancréatique, étude des sécrétions externes et internes du pancréas, *Rev de méd*, Paris 50 231-245, 1933

15 Wohlgemuth, J. Zur Therapie der Pankreasfistel nebst Bemerkungen über den Mechanismus der Pankreassekretion während der Verdauung, *Berl klin Wchnschr* 45 389-393, 1908

6 *The Mixed Meal*—A meal containing the average amounts of fat, carbohydrate and protein of the ordinary general hospital diet was given. The meal was finished in fifteen minutes, and observations were carried on for an additional twenty minutes. A slight rise in rate of flow and a slight fall in total base were noted (chart 7)

Comment According to Pavlov, when pure foodstuffs are given and the volume of pancreatic juice secreted is observed in experimental animals, it is found that the greatest amount follows the giving of carbohydrate, a less amount follows that of protein and the least amount of all that of a fat meal. In human beings the findings have been more variable, but in general they have tended to parallel, in the main, the

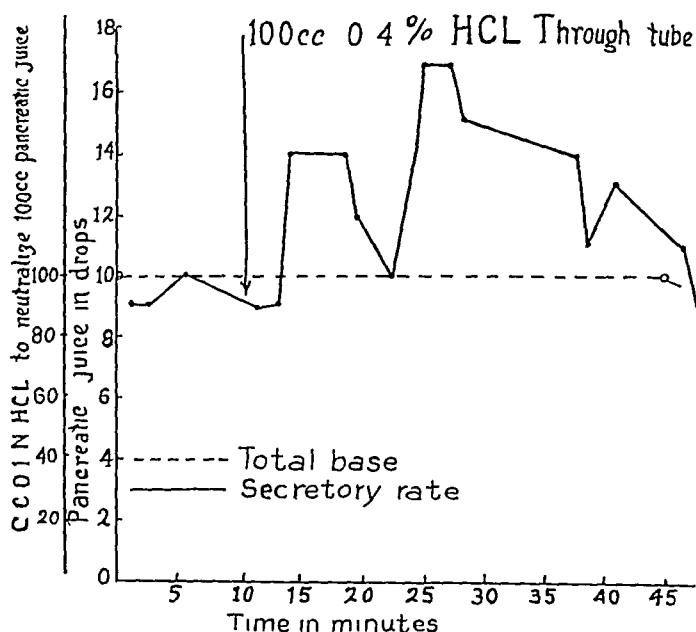


Chart 4—The effect of hydrochloric acid on the external secretory function of the human pancreas

results in animal experiments. In the majority of the studies of human beings the diets used have been mixed, with one or another of the primary foodstuffs predominating. Wohlgemuth¹⁵ stated as his conclusion that the secretory curve after a mixed meal is a composite of the individual food constituents making up the meal.

7 *Hydrochloric Acid*—One hundred cubic centimeters of 0.5 per cent solution of hydrochloric acid was given through a Rehfuess tube introduced directly into the jejunum. A sharp rise in rate of secretion from 9 to 13 drops a minute was noted. There was no change in total base (chart 4).

Comment Bayliss and Starling have shown that the introduction of acid into the duodenum of animals causes a rise in rate of flow, and

they said that this phenomenon could be accounted for by the stimulation to secretin formation thus caused. Sawitsch¹⁶ and Ciminata¹⁷ found that the flow induced by hydrochloric acid is richer in alkali but poorer in ferments and that the so-called "nervous" type of secretion is poorer in alkali but richer in ferments. Our results differed from these results of experiments performed on animals, in that the total base was not affected.

8 *Peptone*—One hundred cubic centimeters of 10 per cent solution of peptone was given through the tube. The secretory rate rose rapidly from 5 to a maximum of 11 drops a minute and later fell again to 5 drops a minute. There was no change in the total base (chart 7).

Comment. Popielski,¹⁸ working with dogs, reported a diminished effect of gastric juice in evoking pancreatic secretion by inactivating hydrochloric acid with peptone. Hydrochloric, sulfuric, phosphoric, oxalic, acetic, tartaric and citric acid all had their effects weakened ten to twelve times by the addition of peptone. In all cases the activity of the acids in evoking pancreatic secretion was proportional to the hydrogen ion concentration.

9 *Sodium Bicarbonate*—Sodium bicarbonate produced no significant change in rate (a fall from an average of 5 to 4.5 drops per minute) but a definite elevation in total base occurred, followed later by a fall below the previous level (chart 5).

Comment. Some observers have noted an inhibitory effect after exhibiting sodium bicarbonate, but Karewski,¹⁹ Pavlov² and Glaessner and Popper²⁰ have denied that it has any effect on pancreatic secretion. The use of sodium bicarbonate in conjunction with a diet low in carbohydrate is an integral part of the method advocated by Wohlgemuth as an aid to encouraging closure of a pancreatic fistula.

10 *Coffee*—Coffee caused a delayed rise in rate and an increase in total base from 38 to 84 (chart 7).

11 *Bile Salts*—Bile salts caused a fall in rate and in total base (chart 7).

Comment. Ivy and Lueth²⁰ and Mellanby²¹ reported an increase in the flow of pancreatic juice after the exhibition of bile.

16 Sawitsch, W. W. Beiträge zur Physiologie der Pankreassaftsekretion, Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs. **4** 1-18, 1909.

17 Ciminata, A. La secrezione esterna del pancreas dopo esclusione pilorica e gastro-digiunostomia a Y di Roux, Arch. di fisiol. **23** 304-317, 1925.

18 Popielski, L. Die Wasserstoffionen und die sekretorische Tätigkeit der Bauchspeicheldrüse, Arch. f. d. ges. Physiol. **174** 152-176, 1919.

19 Karewski, F. Zur Diagnose und Therapie der Pankreascysten, Deutsche med. Wchnschr. **16** 1035-1037, 1890.

20 Ivy, A. C., and Lueth, H. C. On Bile Stimulation of Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **24** 837, 1927.

21 Mellanby, John. Mechanism of Pancreatic Secretion, Lancet **2** 215-218 1926.

12 *Magnesium Sulfate*—Thirty cubic centimeters of a 15 per cent solution of magnesium sulfate caused no appreciable change in either rate or total base (chart 7)

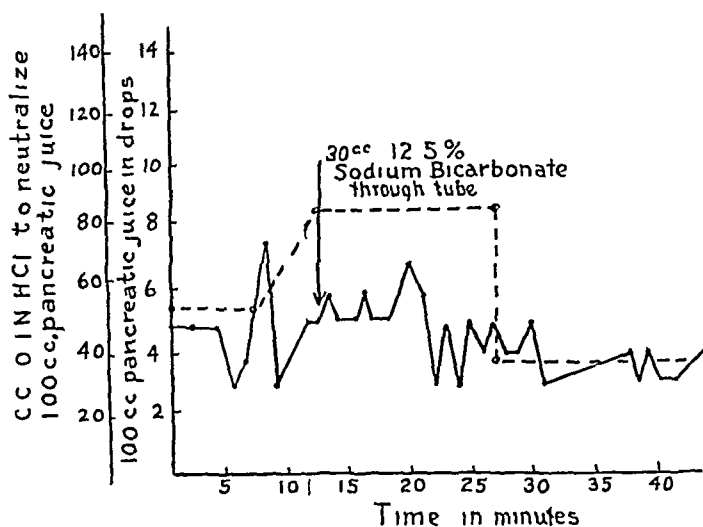


Chart 5—The effect of sodium bicarbonate on the external secretory function of the human pancreas

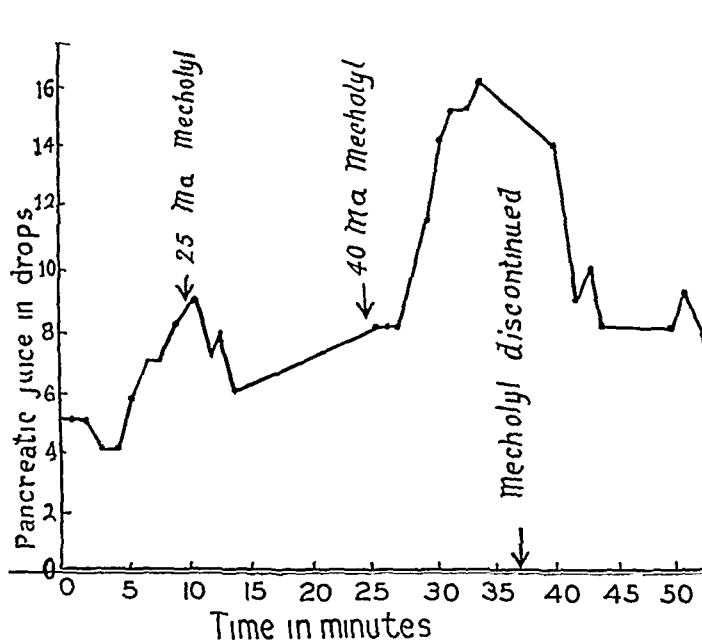


Chart 6—The effect of mecholyl on the external secretory function of the human pancreas

13 *Mecholyl*—One-tenth per cent mecholyl was given by iontophoresis, the electrodes being placed on the front and back of the thorax. With 25 milliamperes of current, the rate of secretion rose from 5 to 8 drops a minute. After fifteen minutes the current was raised to 40

milliamperes, and the rate increased sharply to a maximum of 16 drops a minute. The current was discontinued twenty-seven minutes after the experiment was begun, and the rate returned to normal fifteen minutes later (chart 6).

Comment Mecholyl exerts an excitatory effect on the parasympathetic innervation. This drug proved to be the most powerful stimulus to the flow of pancreatic juice of any used in our experiments. The effect noted is due, we believe, to stimulation of the parasympathetic nerve fibers supplying the pancreas.

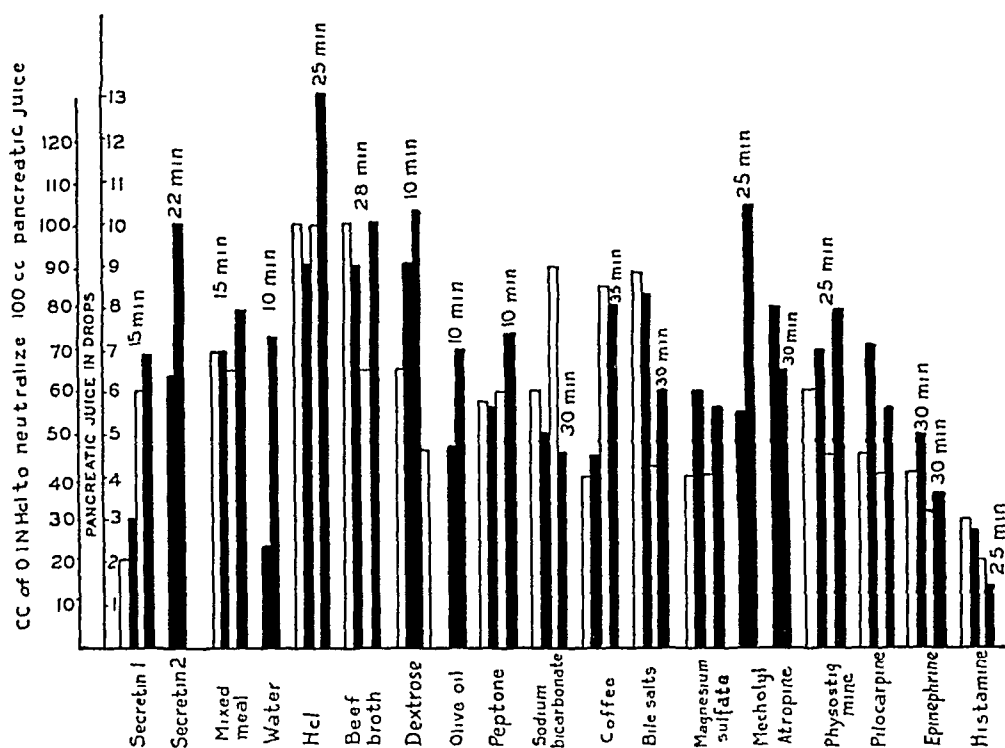


Chart 7—Summarizing the effect of the administration of various substances on the total base and on the rate of secretion of human pancreatic juice. The white columns indicate the total base before and after the onset of the experiment. The black columns indicate the secretory rates before and after the onset of the experiment. The time of maximum duration is indicated above the columns.

14 *Atropine*—Atropine, $\frac{1}{100}$ grain (0.006 Gm), was given intramuscularly. A slight fall in rate occurred after ten minutes. The total base was not measured (chart 7).

Comment Atropine has been found to diminish the secretion.²² Snyder and Lum, besides reporting a diminution caused by atropine, stated that the expected hourly rise after meals was converted into a fall which lasted about an hour.

²² Villaret, M., and Justin-Besançon, L. *Physiologie de la sécrétion pancréatique de l'homme étudiée par la fistulisation du canal de Wirsung*, *Nutrition* 6:209-222, 1936. Weaver, Luckhardt and Koch.^{9b} Glaessner.¹⁰ Holst.^{9d}

15 *Physostigmine*—Physostigmine, $\frac{1}{50}$ grain (0.0013 Gm.), was given intramuscularly. No effect was noted for thirteen minutes, when a gradual rise in secretory rate began. The total base fell from 60 to 40 (chart 7).

16 *Pilocarpine*—After an injection of $\frac{1}{8}$ grain (0.008 Gm.) of pilocarpine hydrochloride into the muscle, both rate and total base fell slightly (chart 7).

Comment. The rise following the administration of physostigmine was anticipated. The negative results with pilocarpine were contrary to the effects obtained by others.²³ Snyder and Lium obtained a striking increase in rate of flow with much smaller doses of pilocarpine and physostigmine.

17 *Epinephrine*—When epinephrine hydrochloride (0.005 Gm.) was given intramuscularly, a fall in rate began in five minutes and reached an average of 2 drops a minute, which was maintained for twenty-five minutes, the total base fell from 40 to 28 (chart 7).

Comment. These results are in accord with those of Anrep,²⁴ who obtained a fall in rate of flow by stimulation of the splanchnic nerves.

18 *Histamine*—After the intramuscular injection of 0.0005 Gm. of histamine phosphate there was no significant change in rate, and there was only a slight fall in the total base (chart 7).

SUMMARY

Physiologic observations on the external secretory function of the human pancreas were made on a patient in whom a pancreatic fistula developed after a Billroth II type of gastric resection. The fistula was later successfully transplanted to the anterior wall of the stomach. Preceding the operation the effect on the rate of secretion and on the total base was determined before and after the administration of various drugs and foodstuffs.

The volume of pancreatic juice secreted in twenty-four hours was estimated at 600 cc. A rise in secretory rate (chart 7) followed the exhibition of secretin, a mixed meal, water, hydrochloric acid, beef broth, dextrose, olive oil, peptone, coffee, mecholyl and physostigmine. A fall in the secretory rate occurred after the exhibition of sodium bicarbonate, bile salts, magnesium sulfate, atropine, epinephrine and histamine. The total base was elevated after the administration of secretin, sodium bicarbonate and coffee and was depressed after the administration of a mixed meal, beef broth, dextrose, bile salts, physostigmine, epinephrine

²³ Sawitsch.¹⁶ Snyder and Lium.⁷ Villard and Labry.¹²

²⁴ Anrep, G. V. The Influence of the Vagus on Pancreatic Secretion, *J. Physiol.* **50** 421-433, 1915-1916.

and histamine. There was no significant change in total base after the exhibition of hydrochloric acid, peptone and magnesium sulfate.

The literature on pancreatic fistula as far as it deals with similar observations on the physiology of the human pancreas has been reviewed, and the results of the investigations of others have been compared with our own results.

Dr W T Coughlin, Professor of Surgery, St Louis University School of Medicine, assisted in an advisory capacity.

ABSTRACT OF DISCUSSION

DR HOWARD M CLUTE, Boston. Dr McCaughan is to be complimented not only on the valuable physiologic studies that he has made of his two patients with pancreatic fistula but also on the excellent results obtained with surgical treatment.

From the point of view of the general surgeon it is interesting to consider the method by which, in the course of gastric and pancreatic surgical treatment, pancreatic fistula is caused. In my experience with patients with acute pancreatitis in which a drain has been inserted into necrotic pancreatic tissue, a permanent pancreatic fistula has not resulted, although transient drainage of pancreatic secretion may occur.

In a recent case in which subtotal pancreatectomy was performed no escape of pancreatic fluid from the wound postoperatively was observed, although at operation I removed more than half the pancreas. In cases of resection of the stomach I have not seen the occurrence of postoperative fistula, although I have often taken out superficial portions of the pancreas with the tumor.

It appears to me that pancreatic fistula tends to develop when surgical intervention obstructs the main pancreatic duct and that no permanent fistula formation follows injury of only the pancreatic parenchyma.

After drainage of the biliary tract in acute pancreatic necrosis, the emptying of pancreatic secretion through the major duct is resumed in those cases in which recovery is obtained, and since the major duct is intact, no fistula forms. In partial resection of the pancreas the major and minor ducts are tied off at their distal ends, but nothing interferes with drainage through their proximal portions, hence a fistula does not form.

In cases of gastric resection, however, a different situation may arise owing to injury at operation either of the accessory duct of Santorini or even of the major pancreatic duct. Surgeons should realize that the accessory pancreatic duct may enter the duodenum as much as 1 inch (2.5 cm) above the level of the papilla of Vater. When the duodenal stump is closed, therefore, after gastric resection, especial pains should be taken that the accessory pancreatic duct is not cut. I have shaved off the surface of the pancreas during gastric resection and have left large raw areas of pancreas without having a fistula form. I believe that injury to the pancreatic ducts themselves is necessary to fistula formation.

It is interesting to inquire why pancreatitis does not follow the transplantation of a pancreatic fistula into the stomach. Commonly bouts of cholangitis follow anastomosis of the gallbladder and the stomach, yet there is no pancreatitis in cases in which the pancreas drains directly into the stomach after a fistula is transplanted. It is of course true that the pancreatic secretion is continuous both by day and by night, but this in itself does not seem an adequate explanation of

the problem Further information on this subject may well be applied to cases of biliary intestinal anastomosis in the prevention of postoperative infection of the biliary tract

DR WILLIAM T COUGHLIN, St Louis As I listened to Dr McCaughan I was reminded of Beaumont, who took advantage of opportunity when it presented itself I wish to compliment Dr McCaughan on the zeal, care, skill and efficiency with which he has carried out his experiments The amount of work is appalling, especially from the standpoint of an older man This is a young man's work

Several years ago, when some one was asked to discuss surgery of the pancreas, he said, "Well, it's a good deal like discussing the hepatology of Ireland" There was not much surgery of the pancreas Now, through the efforts of the younger investigators, who are being trained in chemistry and physiology, the problems are gradually being solved There is a considerable amount of surgical treatment of the pancreas today

Treatment of the fistula has given surgeons trouble for a long time Transplantation of the fistulous tract has been done for fistula of the common duct for many years, but it has not always been successful, the reason being that the tract is most often a tube of connective tissue, not lined with epithelium, and will probably continue to shrink As time goes on there is danger that the condition will recur and lead to cyst formation, abscess or some other complication

The secretion of the pancreas is necessary to life, and it is estimated that the amount secreted daily is about 400 cc It is not, then, dehydration that kills the patient with a large fistula but a loss of the chemicals contained in the large amounts of secretion So far the biochemists have not been able to supply substitutes for everything that the pancreas furnishes the organism, but they are on the way, and I think that soon it will be possible to remove the pancreas in toto for cancer and give the patient something as a substitute, unless Dr Rowntree and his associates make all surgical treatment of cancer unnecessary

The story of cancer of the pancreas is disheartening from a surgical standpoint, and the cysts, the traumas and the fistulas just about completed the series of successful surgical conditions until recently, when adenoma of the pancreas was brought to attention If the medical workers and the chemists will do what surgeons require of them, I feel certain that with the younger investigators coming along the way they are, it will not be long before surgeons can do anything required with regard to the pancreas

DR JOHN J GILBRIDE, Philadelphia My experience in this regard has been limited to a study of a few of my own patients with pancreatic fistula, some patients seen through the courtesy of the late Dr John B Deaver, with whom I made the rounds of the wards for years at Lankenau Hospital, and some experimental work on dogs

The management of pancreatic fistula is a difficult task In these cases the course was violent, being characterized by severe local and systemic manifestations—local in the digestive effect on the abdominal wall and general in the effect caused by toxemia, dehydration and acidosis

Treatment consists in the protection of the abdominal wall, administration of alkalis, milk diet and replacement of the body fluids

Many of the cases of pancreatic fistula reported in the literature do not appear to me to be of this type, largely because of the mild and prolonged course, in some of them extending over a year or two That is not the course of pancreatic fistula in my experience According to what I have seen of so-called fistulous tracts in the human being, the wall is formed by the adjacent organ, and there is

not a definite, fibrous, separate-walled tract. Furthermore, in my opinion, it is absurd to speak of the transference of the wall of a fistulous tract. A fistula is controlled by attacking it at its source and not by attacking it at its termination, moreover, a fistulous tract will close of its own accord when its cause has been removed.

DR ROLF LIUM, Boston. I have seen two patients with pancreatic fistula. One was in a man of 45 who had had local resection for carcinoma of the ampulla of Vater. Dr. Beth Vincent performed this operation, and in the course of the procedure the duct of Wirsung was cut across. A catheter was inserted into the duct, and brought out transduodenally and through the abdominal incision. In the eleven days following the operation it was possible to collect pure pancreatic juice, which varied in amount from 200 to 1,400 cc in twenty-four hours. The latter figure is the largest amount of pancreatic secretion that has ever been obtained from the fistula of a human being.

The other patient was a boy with traumatic rupture of the pancreas. The pancreatic bed was drained after abdominal exploration, and a fistula became established which drained 500 cc a day. He had several attacks of epigastric pain, nausea and vomiting, with tumor formation, all of which subsided on reestablishment of the fistula. When he entered the Lahey Clinic, four months after the original injury, he was placed on the Wohlgenuth regime. This produced a diminution in quantity of secretion to about 150 cc a day, but once the reduction had been effected, the secretion remained at a plateau level and showed no evidence of further reduction.

Dr. Lahey performed a pancreatojejunostomy which was successful. Six months later the patient, while playing baseball, was again struck in the abdomen, and because of the severe pain another exploratory operation was performed. The line of anastomosis was perfectly intact, and definite injury was not demonstrated.

A pancreatic fistula arises after some types of surgical procedure in the neighborhood of the pancreas, and in 60 to 80 per cent of cases it follows marsupialization and drainage of a pancreatic cyst. This type of treatment has the sanction of long usage, but it is not the only method that has been tried. I have found reports by various authors of twelve cases in which primary anastomosis was effected between a pancreatic cyst and the digestive tract. In six cases pancreatogastrostomy was performed, in two cases each pancreatoduodenostomy and pancreatocholecystostomy and in one case pancreatojejunostomy. The operative mortality was zero, and all the patients were well after operation. One patient died of pulmonary tuberculosis seven weeks after operation, and the pancreatic cyst had shrunk from the size of a child's head to that of a walnut. No retrograde infection of the pancreas occurred.

In view of these cases I believe that primary anastomosis between a pancreatic cyst and the gastro-intestinal tract should be part of the surgical treatment of this condition. It will save the surgeon and the patient the trouble of a post-operative fistula, and in certain instances it will avoid a secondary operation for transplantation.

DR A. C. ILL, Chicago. I should like to correct a statement made by the last speaker. Secretin has been injected intravenously into human beings by three other groups of workers, and it has been found to be active, as a matter of fact, it has been suggested by two different groups as a means of testing pancreatic function.

I have frequently been asked questions pertaining to the care of the patients with a pancreatic fistula, particularly in cases in which a great deal of digestion of the abdominal wall occurs. What can be done to decrease the production of pancreatic juice? I was interested in Dr McCaughan's report primarily from the point of view of inhibitors of pancreatic secretion. I gathered, as I followed his slides, that according to his observations atropine is probably the best drug for that purpose. My colleagues and I have been giving the question considerable attention in our laboratory this past year, and Dr Craft has found that ephedrine given subcutaneously is the best drug for reducing the pancreatic secretion in the dog, as a matter of fact, if 10 mg of ephedrine is given subcutaneously every two hours, the pancreatic secretory response to a meal can be decreased by 50 per cent. We use silicon dioxide gel as a dressing powder. As to diet, the Wohlgemuth recommendation is the best, namely, a low carbohydrate, medium protein and high fat diet, with sodium bicarbonate.

DR J M McCAUGHAN, St Louis. I agree with Dr Lium's discussion of the principles of treatment in these cases.

I should like to show again a slide that I put on before demonstrating the resection of the distal third of this stomach. It might be expected, of course, that this resection would interfere with gastric motility, and also one might expect that the various substances when injected into the stomach would pass into the jejunum rather than into the duodenum and that the effect quantitatively and qualitatively on the pancreas might indeed be different. That is partly unanswerable. However, I believe that Dr Ivy has done some work in which he has brought up a loop fistula in dogs, the so-called Thiry-Vella fistula, and has then applied to the jejunum some of the same substances, particularly mineral acids and fats. He has shown that when a transplant of the pancreas is made subcutaneously, secretion of pancreatic juice takes place when these materials are applied to the jejunum. As can be seen, such a transplant is entirely free from any nerve or vascular connection with the duodenum.

LIPOPENIA ASSOCIATED WITH CHOLESTEROL ESTERSTURZ IN PARENCHYMATOUS HEPATIC DISEASE

ELDON M BOYD, M D, C M

AND

W FORD CONNELL, M D, C M, M R C P (LOND)

KINGSTON, ONTARIO, CANADA

In 1926 Thannhauser and Schabel,¹ developing the observation made by Feigl about eight years previously, found a considerable decrease in the ratio of ester to total cholesterol of blood in parenchymatous hepatic disease. To this phenomenon they gave the name cholesterol *Estersturz* and said they considered that it was due to impairment of the liver in a postulated synthesis of cholesterol esters.

Since that time controversy has arisen regarding not only the correctness of the interpretation but even the validity of the actual findings in the blood. Most of the clinical evidence pro and con has been reviewed by Gardner and Gainsborough² and by Epstein,³ and the experimental angle has been discussed by Chanutin and Ludwig⁴ in a paper which constitutes a valuable contribution to the subject. Much of the disparity in clinical observations and a good deal of the disparity even in the more controllable experimental work on animals have been due to the failure of investigators to take into account factors other than damage to the liver which affect the concentration of cholesterol bodies and other lipids in blood. One of the commonest of these other factors is fever, which has a definite lipopenic effect if of any duration.

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This work was aided financially by a grant from the Alice F Richardson Fund of the Kingston General Hospital

1 Thannhauser, S J, and Schabel, H. Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunction. *Klin Wchnschr* 5:252-257, 1926

2 Gardner, J A, and Gainsborough, H. Blood Cholesterol Studies in Biliary and Hepatic Disease, *Quart J Med* 23:465-483, 1930

3 Epstein, E Z. Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, *Arch Int Med* 50:203-222 (Aug) 1932

4 Chanutin, A, and Ludwig, S. The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, *J Biol Chem* 115:1-14, 1936

but which may be lipemic in its early stages⁵ The weight of available evidence indicates that in uncomplicated parenchymatous disease of the liver there occurs a decrease in plasma ester cholesterol, with variable changes in plasma-free cholesterol, and hence that there is a more significant decrease in the ratio of ester to total cholesterol In uncomplicated obstructive jaundice, on the other hand, the common finding is hypercholesterolemia The determination of ester and total cholesterol has therefore been advocated, especially by Epstein,³ as a diagnostic aid in differentiating obstructive from nonobstructive jaundice

Gardner and Gainsborough² stated the opinion that the *Esterstunz* is due to failure of absorption of cholesterol and fat from the intestine in the absence of bile, because they found a low ester—total cholesterol ratio in cases of biliary fistula Hawkins and Wright⁶ said they disagreed with this conclusion because they obtained a low ratio even though bile was present in the stools Thannhauser and Schaber¹ originally postulated that the condition is due to failure of the liver to synthesize cholesterol esters at the normal rate

Many of the interpretations of the changes in cholesterol metabolism are rendered futile by failure to consider cholesterol as an inherent part of lipid metabolism Cholesterol binds with fatty acids to produce cholesterol esters, and these esters are undoubtedly under the influence of factors which affect lipid metabolism Cholesterol admittedly may function beyond the realm of lipids, but this does not justify its isolation from lipids, as apparently implied by Gardner and Gainsborough² ("Cholesterol and its derivatives are too often lumped together with fats, lecithides, etc., with which they have not the slightest chemical connexion, under the misleading term 'lipoid'") In the present work it was found that the cholesterol *Esterstunz* of parenchymatous hepatic disease was in reality part of a general lipopenia, a finding which must certainly be considered in evaluating any explanation

The present work comprised a study of twenty-seven patients with nonobstructive jaundice or bilirubinemia from the medical divisions of the Kingston General Hospital A variety of hepatic conditions was included in this group, such as hepatic cirrhosis, congestion of the liver, catarrhal jaundice, arsphenamine poisoning and hepatic toxemia of pregnancy (one case) All the patients exhibited in common bilirubinemia, with a plasma cholesterol *Esterstunz* and no evidence of increased body temperature or any other condition apart from the hepatic disturbance which is known to affect the concentration of plasma lipids Blood was obtained during fasting and oxalated Extracts of the plasma and of the red blood cells were immediately prepared by the method of cold dilution, and the extracts were analyzed by a modification of the oxidative micromethods of Bloor, as used in previous studies⁵ The results obtained have been summarized statis-

5 Boyd, E M The Lipopenia of Fever, *Canad M A J* **32** 500-506, 1935

6 Hawkins, W B, and Wright, A Blood Plasma Cholesterol Fluctuations Due to Liver Injury and Bile Duct Obstruction, *J Exper Med* **59** 427-439, 1934

tically in tables 1 and 2, in which the values for normal adults are those previously obtained by these same methods ⁷

Accompanying the cholesterol *Estersturz* of hepatic disease there was found to be statistically significant lipopenia (table 1) analogous to the lipopenia of fever ⁵ and of hyperthyroidism ⁸ The average values

TABLE 1—*Lipopenic Changes in Plasma Associated with Cholesterol Estersturz in Parenchymatous Hepatic Disease*

Value	Composition of Total Lipid*						
	Total Lipid	Neutral Fat	Total Fatty Acid	Cholesterol			Phospho lipid
				Total	Ester	Free	
Normal Adults							
Arithmetical mean	617	154	362	181	128	53	195
Standard deviation	75	77	62	22	23	10	37
Coefficient of variation	12	50	17	12	18	19	19
Adults with Parenchymatous Hepatic Disease							
Arithmetical mean	390	133	237	105	65	40	102
Standard deviation	59	68	45	21	22	11	33
Coefficient of variation	15	51	19	20	34	27	32
Average percentage decrease from normal	37	14	35	42	49	25	48
Mean subtracted from normal mean	227	21	125	76	63	13	93
Standard deviation plus normal standard deviation	134	145	107	43	45	21	70

* The lipid values are expressed in milligrams per hundred cubic centimeters of plasma

TABLE 2—*The Lipid Content of the Red Blood Cells in Parenchymatous Hepatic Disease Associated with Cholesterol Estersturz in Plasma*

Value	Composition of Total Lipid*						
	Total Lipid	Neutral Fat	Total Fatty Acid	Cholesterol			Phospholipid
				Total	Ester	Free	
Normal Adults							
Arithmetical mean	598	93	373	140	6	140	361
Standard deviation	62	42	41	32	9	26	56
Coefficient of variation	10	45	12	23	150	19	15
Adults with Parenchymatous Hepatic Disease							
Arithmetical mean	708	55	371	184	50	134	426
Standard deviation	152	52	78	53	51	15	87
Coefficient of variation	22	95	21	29	102	11	20

* The lipid values are expressed in milligrams per hundred cubic centimeters of red blood cells

of lipids in plasma were decreased from 14 to 49 per cent. The most marked decrease was noted in the total and ester cholesterol and phospholipid values, all three of which were lowered by 40 to 50 per cent, on the average. The total lipid and total fatty acid values fell by a

⁷ Boyd, E. M. The Lipemia of Pregnancy, *J. Clin. Investigation* **13** 347-363, 1934

⁸ Boyd, E. M., and Connell, W. F. The Lipopenia of Hyperthyroidism, *Quart. J. Med.* **6** 231-239, 1937

mean of 30 to 40 per cent. Lesser average decreases were recorded in the concentrations of plasma neutral fat and free cholesterol, but these mean changes were not found to be statistically significant.

A statistically significant difference from normal in these results may be concluded to exist if the sum of the standard deviations of two corresponding means is less than the difference between the means. The differences between the means for plasma and the sum of the standard deviations of these same means are given in the last two lines of table 1. When the figure in the last line is less than the figure immediately above it, a significant change from normal may be concluded to have occurred in the concentration of that particular lipid. With this criterion of significance, there was found to be a real decrease in the total lipid, total fatty acid, total cholesterol, ester cholesterol and phospholipid contents of the plasma of these patients. There was not a significant decrease in the amount of free cholesterol and neutral fat. The data given in table 1 demonstrate just as clearly as if the results had been reported in toto that in parenchymatous hepatic disease associated with cholesterol *Estersturz*, many values for plasma neutral fat and free cholesterol may be found within as well as below the normal range but that practically all values for the other lipids of plasma are below the normal range.

To compare with normal the relative variations of lipid values in this type of hepatic disease, coefficients of variation have been calculated for each lipid. The coefficient of variation was determined by multiplying the standard deviation by 100 and dividing by the mean; it represents the standard deviation expressed as a percentage of the mean. The relative variation of the plasma total lipid, neutral fat and total fatty acid contents was about the same as normal, but there was 40 to 90 per cent more variation than normal in the values for the cholesterol fractions and phospholipid.

Coincident with the occurrence of lipopenic changes in the plasma, the lipid content of the red blood cells was found to be elevated in a number of instances, but this did not occur consistently enough to be labeled as statistically significant. These results are summarized in table 2. There were increases in the mean value of total lipid, total fatty acid, total cholesterol, ester cholesterol and phospholipid and a mean decrease in neutral fat and free cholesterol. In no instance was the sum of the standard deviations less than the difference of the means. This indicates that many of the values were within the normal range, which was precisely the case. As seen by the coefficients of variation, most of the values were considerably more variable than normal. It may be concluded that in parenchymatous hepatic disease with associated cholesterol *Estersturz*, instances occur in which there is an

increased lipid content of the red blood cells but that this does not occur in all or in a considerable majority of cases

The results in one or two cases merit further discussion. A young man, a university student with a history of frequent occurrence of jaundice in his family, was admitted to the hospital with jaundice, grayish stools, slight fever and an icteric index of 30. The temperature rapidly subsided with recovery of the patient, and a few days later lipid analysis revealed 90 mg per hundred cubic centimeters of free and no ester cholesterol in the plasma. The plasma phospholipid content was 52 mg per hundred cubic centimeters, but the neutral fat value was markedly elevated, to 305 mg per hundred cubic centimeters, and the plasma was distinctly milky. The nonoccurrence of ester cholesterol in human plasma has previously been reported¹ but is rare.

A second interesting case was that of a married woman (tripara) aged 24 with hepatic toxemia of pregnancy. No values for plasma lipids have previously been reported in this rare condition. The patient was eight months pregnant when admitted to the hospital. She had been vomiting regularly for nearly a month and was slightly jaundiced. She had vague pains in the legs, areas of paresthesia on the hands and exaggerated reflexes. The blood pressure was normal, and the urine contained 1+ albumin, acetone, diacetic acid, bile and a few casts. The blood showed an elevated urea content (46 to 66 mg per hundred cubic centimeters), a low plasma albumin content (2.7 Gm per hundred cubic centimeters) and an icteric index varying between 18 and 36, but normal dextrose and uric acid contents and a normal carbon dioxide-combining power. Analysis of the plasma revealed a total lipid content of only 413 mg per hundred cubic centimeters, less than half that normally expected at this time, since the patient should have shown, if normal, lipemia of pregnancy.⁷ The following values were noted: 68 mg of neutral fat, 227 mg of total fatty acid, 123 mg of total cholesterol, 63 mg of ester cholesterol, 60 mg of free cholesterol and 180 mg of phospholipid per hundred cubic centimeters of plasma. All these values are subnormal for a pregnant woman near term,⁷ except the phospholipid and free cholesterol values, which were about what might be found normally. The case is of interest as being the first recorded instance of a complete differential lipid analysis of plasma in hepatic toxemia of pregnancy.

The next question for consideration concerns the interpretation that can reasonably be placed on these results in cases of parenchymatous disease of the liver. Gardner and Gainsborough,² from studies of cholesterol alone, said they considered that the decrease in plasma cholesterol esters was due to failure of proper absorption of cholesterol and fat from the intestine in the absence of bile. While Hawkins and

Wright⁶ said they discounted this explanation with the finding of bile in the stool together with a low plasma ester value, the present results show further that this theory is untenable. One could scarcely conceive of impaired intestinal absorption simultaneously lowering the plasma content of cholesterol esters and phospholipid but having no effect on free cholesterol and neutral fat. During the absorption of sufficient quantities of fat by the intestine, all plasma lipids, especially neutral fat, are increased in value.

The original explanation of Thannhauser and Schaber,¹ that cholesterol esters are decreased in plasma because damage to hepatic cells hinders one of their functions in synthesizing esters from cholesterol and fatty acids, appears to be the most reasonable theory to account for the results. Cholesterol esters are not stored to any extent in normal tissues, although they are apparently synthesized as a by-product in degenerating tissue.⁹ A lessened production of cholesterol esters would thus soon result in a diminution in their concentration in the plasma, the only medium in which they are found in any quantities. Thannhauser and Schaber¹ have argued that since damage to the liver lowers the plasma content of cholesterol esters, it is likely that these substances are produced in the liver. Supporting this is the fact that cholesterol esterases have been found in the liver.

The theory that hepatic damage is the cause of the decrease in plasma ester cholesterol is further substantiated by the fact that the same theory may be invoked to explain the decrease in phospholipid of plasma found herein and found experimentally by Chanutin and Ludewig.⁴ The liver has been postulated by many, more recently by Sinclair,¹⁰ as a probable site of the synthesis of phospholipids. Accepting this, it is reasonable to find that in parenchymatous hepatic disease the plasma content of phospholipid falls, since metabolic phospholipid is also not generally stored in other tissues of the body.¹⁰

It is generally accepted that cholesterol is readily synthesized in many tissues of the body. Neutral fat is present in abundance in practically all tissues of the body, being the storage form of fat. Damage to the liver would not therefore be expected to have any considerable effect on the concentration of either of these substances in plasma. Any decrease which does occur is probably due to the presence of insufficient phospholipid to aid in the colloidal solution of these aqueous insoluble substances.

9 Boyd, E. M. The Relation of Lipid Composition to Physiological Activity in the Ovaries of Pregnant and Pseudopregnant Rabbits, *J Biol Chem* **108** 607-617, 1935.

10 Sinclair, R. G. Fat Metabolism, in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif, Stanford University Press, 1937, vol. 6, pp 245-268.

Assuming that a dynamic equilibrium exists between lipids in plasma and lipids in tissues, impairment of hepatic function would thus result in a gradual decrease in plasma phospholipid and cholesterol ester contents but would not necessarily affect the content of free cholesterol and of neutral fat. This appears to be the most likely explanation of the results obtained herein, but it is advanced as a working hypothesis, not as a proved theory.

A point which is difficult to bring into line with this hypothesis is the accumulation of fat and cholesterol esters in the liver in certain conditions (acute yellow atrophy, depancreatized insulinized dogs) in which the plasma content of cholesterol esters falls¹⁰. The latter cholesterol esters may represent esters produced as a result of degeneration, as in the ovary,⁹ rather than metabolic esters, but why such esters do not readily diffuse into the plasma is a question. The fact that administration of choline and some related compounds relieves the fatty infiltration of the liver and brings the lipopenic plasma value to normal in experimental animals suggests that the synthesis of phospholipid and the synthesis of cholesterol esters in the liver may be in some manner interrelated.¹⁰

SUMMARY

A statistically significant decrease, averaging 35 to 49 per cent, was found in the concentrations of plasma total lipid, total fatty acid, total and ester cholesterol and phospholipid in twenty-seven cases of parenchymatous hepatic disease with associated cholesterol *Estersturz*. Lesser average decreases in the plasma neutral fat and the free cholesterol content were noted but were not found to be statistically significant.

Occasionally, increased amounts of lipid were encountered in the red blood cells, but in other cases the values were within the normal range, and there was no change in the red blood cells which was characteristic for the entire group.

A case in which there was no plasma ester cholesterol and a case of hepatic toxemia of pregnancy are reported.

STUDIES ON PORPHYRIA

III ACUTE IDIOPATHIC PORPHYRIA

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The clinical and pathologic aspects of porphyria were extensively reviewed by Mason, Courville and Ziskind¹ in 1933. In the German literature the chemistry of porphyria has recently received considerable attention.² In the American literature recent papers by Dobriner and his associates,³ Watson⁴ and Watson and Clarke⁵ have added important new data. The recent monograph by Waldenstrom⁶ has clarified

From the University of Chicago Clinics, Chicago

1 Mason, V R, Courville, C, and Ziskind, E. Porphyrins in Human Disease, *Medicine* **12** 355, 1933

2 (a) Fischer, H. Ueber Hamin und Porphyrine, *Verhandl d deutsch Gesellsch f inn Med*, Kong 45, 1933, p 7. (b) Waldenstrom, J. Some Observations on Acute Porphyria, *Acta med Scandinav* **83** 281, 1934, (c) Untersuchungen uber Harnfarbstoffe, hauptsachlich Porphyrine, mittels der chromatographischen Analyse, *Deutsches Arch f klin Med* **178** 38, 1935. (d) Waldenstrom, J, Fink, H, and Hoerbarger, W. Ueber ein neues bei der akuten Porphyrie regelmassig vorkommendes Uroporphyrin, *Ztschr f physiol Chem* **233** 1, 1935. (e) Schreus, H T. Ergebnisse und Probleme der Porphyrinforschung, *Klin Wchnschr* **13** 121, 1932.

3 (a) Dobriner, K. Urinary Porphyrins in Disease, *J Biol Chem* **113** 1, 1936, (b) Simultaneous Excretion of Coproporphyrin I and III in a Case of Chronic Porphyria, *Proc Soc Exper Biol & Med* **35** 175, 1936. (c) Dobriner, K, and Rhoads, C P. The Excretion of Coproporphyrin I Following Hemorrhage in Dogs, *J Clin Investigation* **17** 105, 1938, (d) The Metabolism of Blood Pigments in Pernicious Anemia, *ibid* **17** 95, 1938.

4 Watson, C J. Concerning the Naturally Occurring Porphyrins. I The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis. *J Clin Investigation* **14** 106, 1935, II The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces of a Case of Familial Hemolytic Jaundice, *ibid* **14** 110, 1935, III The Isolation of Coproporphyrin I from the Feces of Untreated Cases of Pernicious Anemia, *ibid* **14** 116, 1935, IV The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, *ibid* **15** 327, 1936, V Porphyrins of the Feces, *ibid* **16** 383, 1937.

5 Watson, C J, and Clarke, W O. The Occurrence of Protoporphyryn in the Reticulocytes, *Proc Soc Exper Biol & Med* **36** 65, 1937.

6 Waldenstrom, J. Studien uber Porphyrine, *Acta med Scandinav*, 1937, supp 82.

the diagnostic criteria, the familial occurrence and much of the symptomatology of acute porphyria. The first two papers of the present series of studies⁷ have further introduced the basic chemical nature of the porphyrins and have presented evidence that porphyria may be a persistence of fetal pyrrole metabolism. For these reasons it is not considered necessary in this paper to go deeply into either the clinical or the chemical aspects that have been dealt with in the literature.

The present report of a case concerns what is commonly called acute idiopathic porphyria. Fischer and Libowitzky⁸ have recently reported the first case of acute toxic porphyria with excretion of uroporphyrin I, but the present case is the first one in which this porphyrin has been found in the idiopathic type of the disease. Evidence is presented that the metabolic disturbance is not limited to the period of acute symptoms. The persistence of this metabolic error between attacks and its familial occurrence suggest that acute idiopathic porphyria may be as much an inborn error of pyrrole metabolism as is congenital porphyria.

REPORT OF A CASE

Mrs. E. D., aged 29, a graduate nurse employed in a pediatric hospital, was admitted to the hospital on June 25, 1935.

Complaint—The patient complained of unbearable pains in the head, abdomen, back and extremities, which had been felt for three days.

History of the Present Illness—The exact date of onset of the illness was uncertain. In 1931 pains in the right lower quadrant of the abdomen led to appendectomy. Since 1932 she had suffered from increasing constipation and insomnia. Examination of the blood in 1931 revealed an erythrocyte count of 4,510,000, the hemoglobin value being 90 per cent (Sahli). In 1932, for some reason, a blood count was made, and it showed an erythrocyte count of 4,700,000, with a hemoglobin value of 70 per cent (Sahli). One month later the hemoglobin value (Sahli) was 65 per cent. The patient was given iron and was irradiated with a quartz mercury vapor arc lamp. In two months the hemoglobin value rose to 78 per cent (Sahli), and a dark tan developed. About this time she was told that she was jaundiced, but she paid no attention to it.

On June 16, 1935, she was married. The honeymoon was uneventful. About June 18 she used a douche of saponated solution of cresol. No other drug, medication or alcohol was used at this time. The evening before her marriage she took an enema of tap water. This produced the last defecation until June 30, fifteen days later. On June 21 she began having headache, with nausea and retching. This persisted and became more severe, with vomiting and abdominal cramps.

7 (a) Turner, W. J. Studies on Porphyria. I. Observation on the Fox Squirrel, *Sciurus Niger*, *J. Biol. Chem.* **118**: 519, 1937. (b) Turner, W. J., and Obermayer, M. E. Studies on Porphyria. II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, *Arch. Dermat. & Syph.* **37**: 549 (April) 1938.

8 Fischer, H., and Libowitzky, H. L. Auftreten von Uro- bzw. Koproporphyrin I bei klinischer Porphyrie, *Ztschr. f. physiol. Chem.* **241**: 220, 1936.

Pains spread to the extremities, and after a "fainting spell" on June 25 she was brought to the hospital

Past History—Except for urticaria when a child the patient had always been healthy, active and sociable. For several winters she had suffered from recurrent sinusitis, for which she had used acetphenetidin in small amounts. The last dose of this was taken in December 1934. No other drugs had been taken, and no history of contact with lead could be elicited. In 1930 her blood pressure was recorded as 110 systolic and 80 diastolic. The genito-urinary history revealed no abnormality except moderate dysmenorrhea. She had never noted the color of her urine.

Family History—The data for the patient's family are given in the accompanying diagram.

There is no history of consanguinity in the antecedents of the patient. No member of the family was known to have had a cutaneous eruption. The patient's mother died of carcinoma of the breast.

Specimens of urine from all the living members of the family (twenty-eight) were examined. Only in the urine of the patient and that of her eldest sister

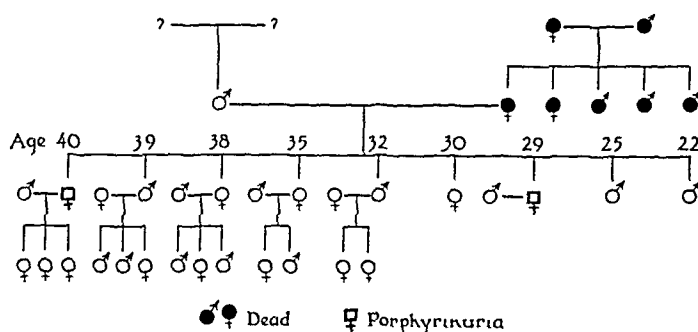


Chart giving the data for the patient's family

was uroporphyrin found. There was no opportunity for direct examination of this sister, so it is not known whether or not she had porphyriopathic symptoms.

Physical Examination—The temperature was 99.4 F, the pulse rate 104, the respiratory rate 24 and the blood pressure 160 systolic and 90 diastolic.

The patient appeared critically ill. She was admitted to the gynecologic service. Although the abdomen was soft, tubal abortion was suspected. The patient was prepared for examination under anesthesia. During the preparation she had two epileptiform convulsions lasting several minutes each, followed by coma of from five to ten minutes. With the patient under ethylene anesthesia no pelvic mass could be found, and operation was deferred.

When the patient was returned to her room the blood pressure was 180 systolic and 100 diastolic. At this time a more complete physical examination was made. It was noted that the complexion was strikingly dirty gray-yellow, with cyanosis of the lips. Between convulsions the patient was too restless for satisfactory examination, but it was seen that the pupils were small, round and equal and reacted well to light. She was able to see, but she failed to recognize old friends. During convulsions the pupils dilated equally and did not react to light. The fundi revealed pallor, but it could not be ascertained whether there was vascular constriction.

The lungs were clear and resonant.

The radial pulse was equal on the two sides, of bounding type and of high tension. The rhythm was regular. There were no murmurs over the heart, and the heart was not enlarged.

The abdomen was soft. There were no palpable masses.

The convulsions were typically epileptiform, with simultaneous loss of consciousness and generalized tonic spasms, opisthotonos, cessation of respiration and mydriasis. There was, however, neither defecation nor urination. From the appearance of the patient, who seemed more markedly excited just before loss of consciousness, it was thought probable that there was an aura. The duration of the attacks was from one to five minutes. As the tonic spasm passed the patient relaxed into coma without having a phase of clonic movements. The coma persisted for from a few minutes to half an hour. In the period of wakefulness she rolled and tossed in bed, oblivious to the presence of others unless she was touched or addressed. She would answer questions, but only after a delay and then often irrelevantly.

She complained bitterly of pains in the abdomen, head, back and extremities and seemed not to find relief in any position. Phenobarbital, scopolamine hydrobromide and morphine were ineffectual.

Course in the Hospital—On the night of entry the patient voided a small amount of urine, reported as being red-brown, with a trace of albumin and a few hyaline casts but no red blood cells. The leukocyte count was 12,200. During a convulsion lumbar puncture was performed, revealing clear fluid under no increase of pressure, with no cells and no increased content of protein. Lumbar puncture two days later also gave normal results.

June 26. The temperature reached 101° F by rectum. The pulse rate was persistently about 120, with a blood pressure of 178 systolic and 110 diastolic. There was another convulsion during the night.

June 27. The dusky green cyanosis was more impressive than before. The patient slept most of the time but could be aroused without much difficulty. She answered questions slowly and incompletely. Toward noon she began to grow restless and to roll around in bed. At 1:55 p. m. she had a convulsion beginning in the left arm and quickly spreading to the right. This lasted about two minutes and was followed by sleep. A few moments later there was a similar attack. The rest of the day convulsions recurred about every ninety minutes, beginning in the left thumb, ascending the arm and then crossing to the right sternocleidomastoid muscle. In some attacks the muscles of the left thigh showed clonic contractions. The patient seemed semistuporous for the first part of each attack but soon became comatose. About 6:15 p. m. she became restless and cried out. After 0.09 Gm. of phenobarbital was given she became quiet, and the convulsions ceased.

On this day the urine was dark red-brown, of such a striking hue as to suggest the presence of melanin. Suspicion of porphyria was aroused, but spectroscopic examination of the urine showed only a diffuse absorption in the blue-violet region.

June 28. The patient looked much better and was able to take liquids. The temperature remained between 100 and 101.8° F., and the pulse rate between 120 and 130. The blood pressure fluctuated between 180 systolic and 112 diastolic and 158 systolic and 112 diastolic. The morning urine was light yellow but became darker on exposure to light.

June 30. The patient was rational and coherent, but her speech was slurred and slow. There was rapid nystagmus on looking to the right or left or upward and there was complaint of blurring of vision. The fundi were normal. Weakness of the left side of the face and definite ataxia and dysidiadochokinesis of the left hand were noted.

The daily urinary output, which had been between 250 and 850 cc, suddenly increased to 1,870 cc, and the evening blood pressure fell to 146 systolic and 100 diastolic. The temperature remained between 100 and 102 F, with a persistently fast pulse rate. The leukocyte count was 11,500, and the erythrocytes numbered 5,160,000 per cubic millimeter.

July 2 Severe pain continued. She was given 10 cc of a 10 per cent solution of calcium gluconate intravenously, with immediate and striking relief. This was of short duration but could be obtained on each repeated injection. The following day she went to sleep during an injection given for pain and restlessness.

July 15 The patient complained that pains were present in the right arm. At this time the diagnosis of porphyria was verified by spectroscopic demonstration of porphyrins in the fresh, light yellow morning urine. After standing the urine turned dark, and the porphyrin spectrum was obscured.

July 24 The patient awoke with paralysis of the right ulnar and radial nerves. After this she improved rapidly. The paralysis cleared quickly.

August 13 The patient left the hospital on the forty-ninth day after entry.

Laboratory Examinations—The Wassermann and Kahn tests were carried out on the blood and spinal fluid and gave negative reactions.

The leukocyte count remained elevated at least until July 20, with a peak of 18,800 on June 29. The differential counts usually showed about 86 per cent neutrophils, 10 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. On June 26 the hemoglobin value was 92 per cent (Sahli) and the erythrocyte count 5,010,000. The nonprotein nitrogen content was 33 mg, and the dextrose content was 155 mg per hundred cubic centimeters. On June 29 the nonprotein nitrogen content was 19 mg and the dextrose content 102 mg. On July 8 the dextrose content was 71 mg, the average normal value for the method. The calcium content was 9.9 mg per hundred cubic centimeters. A special hematologic report on July 10 showed hemoglobin, 85 per cent (Newcomer), erythrocytes, 4,800,000 per cubic millimeter, leukocytes, 10,250, platelets, 340,000, neutrophils, 69 per cent, lymphocytes, 23 per cent, monocytes, 7 per cent, and eosinophils, 1 per cent. On July 27 the reticulocyte value was 0.8 per cent, and the smear was normal. The following day the reticulocytes numbered 1 per cent. The fragility test gave a normal result. The coagulation time was two and one-half minutes, the patient did not bleed.

Roentgenograms, made on June 25, showed marked gaseous distention of both large and small intestine. There was no evidence of a stone in the urinary tract. Complete roentgenologic examination of the spine, long bones and bones of the hands and wrists showed no abnormality.

Stools were examined twice. The first specimens were brown scybala which gave a negative reaction to the benzidine test. The second specimens were similar but were covered with a slight deposit of mucus.

Later Course—Improvement continued, and the patient returned to work. The blood pressure returned to normal and remained there. The skin lost its dirty green cyanotic appearance, but small hard nodules developed deep in the epidermis, with no subjective symptoms. They did not break down but often became infected, clearing up in about a week without scarring. New ones have continued to appear at intervals up to the present. They are apparently intracutaneous cysts.

As the cyanosis disappeared it became evident that the patient had a yellowish pallor, but no test for bilirubinemia was made until December 5. At this time the bilirubin value was 2 mg per hundred cubic centimeters, with an indirect van den Bergh reaction. Meanwhile it had been learned that the patient was excreting in the urine a substance giving a strong positive reaction to aldehyde

(Ehrlich) This will be considered later On Jan 3, 1936, a galactose test was made simultaneously with a bilirubin tolerance test The former showed only a trace of reducing substance excreted in the first hour For the latter, 46 mg of bilirubin was injected intravenously Before the injection the bilirubin value was 13 mg per hundred cubic centimeters It was 23 mg after thirty minutes, 227 mg after one hour, 206 mg after three hours and 164 mg after five hours Normally this method shows total removal of excess bilirubin in four hours⁹

From Nov 24 to 26, 1935, generalized edema developed The eyelids became swollen, and the patient had difficulty in putting on her shoes With the onset of the catamenia on November 26, the knees also became greatly swollen She had shooting pains in the face and arms The flow stopped on November 30, and the symptoms abated

On December 4 physical examination revealed the following The skin was definitely jaundiced Intracutaneous nodules were present on the nape of the neck, forehead and cheeks The areolae of the nipples were large and dark brown There was no hypertrichosis The blood pressure was 116 systolic and 70 diastolic Neurologically there was found only weakness of the hands

On December 16 the blood was again examined The hemoglobin value, as determined by the Van Slyke oxygen-combining method, was 14.96 Gm per hundred cubic centimeters For the same sample of venous blood the erythrocyte count was 4,800,000 The volume of packed red blood cells, determined by the Wintrobe method,¹⁰ was 46.5 cc per hundred cubic centimeters, corrected The mean corpuscular volume was 97 cubic microns, the mean corpuscular hemoglobin value, 31 micromicrograms, and the mean corpuscular hemoglobin concentration, 31 per cent The mean corpuscular hemoglobin value was at the upper limit of normal, that for the mean corpuscular volume was definitely above normal¹¹ Examination of the blood smears revealed nothing abnormal The leukocyte count was 7,200, with 45 per cent neutrophils, 50 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils Fluorescent erythrocytes were not found in fresh unfixed, unstained smears¹² The apparatus used has been previously described^{7a}

The blood serum contained no methemoglobin Attempts to demonstrate porphyrin in serum by direct spectroscopic examination or by the Fischer acetic acid-ether method¹³ failed Hematin could not be detected spectroscopically by means of the cyanhemochromogen method in a 4 cm depth of serum

The patient was given a diet high in carbohydrate, without obvious effect In the last few weeks of February 1936 she complained of pain in the interscapular region, particularly on the right side By that time the jaundice had disappeared

On May 21, 1936, she again began to have abdominal pain and felt tired, and she reentered the hospital on May 28 In this attack, which was milder than the first,

9 Harrop, G. A., Jr., and Barron, E. S. G. The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, *J. Clin. Investigation* **9** 577, 1931

10 Wintrobe, M. M. The Size and Hemoglobin Content of the Erythrocyte, *J. Lab. & Clin. Med.* **17** 899, 1932

11 Wintrobe, M. M. Anemia. Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles, *Arch. Int. Med.* **54** 256 (Aug.) 1934

12 Keller, J., and Seggel, K. A. Ueber das Vorkommen fluoreszierender Erythrocyten, *Folia haemat.* **52** 241, 1934 Watson and Clarke⁵

13 Fischer, H., and Schneller, K. Zur Kenntnis der natürlichen Porphyrine. VI. Verbreitung des Porphyrins in Organen, *Ztschr. f. physiol. Chem.* **135** 253, 1924

she became stuporous and complained chiefly of pain. Three weeks after the onset she suddenly had one convulsion, which was mild. Two days later she suddenly improved, and within a few days she was able to leave the hospital.

Since then she has been well, with a feeling of only moderate tiredness while at work. There is no more jaundice. The urine continues to contain the substance giving a positive reaction to aldehyde (Ehrlich) and still has an excessive amount of porphyrins. The uroporphyrin band at 6,140 angstroms is persistently visible in the fresh urine.

Chemical Studies—During the first acute attack the studies of the urine were limited, and the stools were not examined. A small amount of ether-soluble porphyrin could be found in the urine. The urine was usually light yellow, but on oxidation it became dark red and the porphyrin spectrum was obscured. The chromogen failed to yield the pigment when treatment with nitrous acid preceded oxidation in light and air. This is in sharp contrast to the urochrome chromogen.¹⁴

In the interval between the first and the second attack, repeated studies of the urine and feces were made.

The first examination of stool was carried out by Dr. Konrad Dobriner, who reported such striking paucity of coproporphyrin that its demonstration depended on the use of fluorescence. I later corroborated this finding and also found large amounts of coproporphyrin in the feces.

Since there has been some suspicion that the dark color of the urine in cases of acute porphyria may be due to urochrome or some similar skatole or indole derivative,¹⁵ a liter of fresh yellow urine was once acidified with sulfuric acid and subjected to steam distillation. The distillate showed a weak violet with Ehrlich's aldehyde reagent. It was obvious that this could not account for the intense pigmentation of the urine.

It was learned early that the patient's urine gave a strongly positive reaction to aldehyde (Ehrlich), the red solution showing the following absorption spectrum: I, 572 to 560 (maximum, 565) millimicrons, II, 510 to 488 millimicrons. These and subsequent measurements were made with a Zeiss model C hand spectroscope. On standing the solution became more brownish, the second band becoming stronger. With hydrochloric acid alone the urine turned red-brown, without the appearance of the band at 565 millimicrons. In contrast to this the urine of a patient with advanced cirrhosis of the liver gave a reaction with the following absorption spectrum: I, 560 to 550 (maximum, 555) millimicrons, II, 510 to 488 millimicrons. It seemed likely therefore that at least part of the former reactor was not urobilinogen. This was further corroborated by its insolubility in purified petroleum (petroleum ether) in which urobilinogen is easily soluble.¹⁶ Waldenstrom¹⁷ has noted much the same phenomenon. Further, Watson¹⁸ has recently

14 Herter, C. A. The Relation of Nitrifying Bacteria to the Urochrome Reaction of Nencki and Sieber, *J. Biol. Chem.* **4**: 238, 1908. On Indolacetic Acid as the Chromogen of the "Urochrome" of the Urine, *ibid.* **4**: 253, 1908.

15 Gutstein, M. Fall von Nephrochromeurie, *Ztschr. f. klin. Med.* **43**: 324, 1917. Maasse, C. Auftreten von Skatolfarbstoff im Harn bei Hamatoporphrie, *ibid.* **99**: 270, 1924. Waldenstrom.⁶

16 Watson, C. J. The Average Daily Elimination of Urobilinogen in Health and in Disease, with Especial Reference to Pernicious Anemia, *Arch. Int. Med.* **47**: 698 (May) 1931.

17 Waldenstrom.^{2c, 6}

18 Watson, C. J. Studies of Urobilinogen. II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch. Int. Med.* **59**: 196 (Feb.) 1937.

reported that in some instances urobilinogen-containing urine of patients with hepatic disease gave much the same results

Toward the end of November 1935, 14 liters of urine was collected, acidified with acetic acid and allowed to stand open to the air beneath the hood for the development of color and the precipitation of porphyrins. This urine was filtered, and the filtrate was saved for later study

The precipitate was found to consist largely of dark brown pigment, which obscured much of the porphyrin spectrum when in solution in ammonium hydroxide. This surprising phenomenon has not previously been reported. The pigments were insoluble in acetic or dilute hydrochloric acid but went readily into solution with dilute ammonium hydroxide. Reprecipitation by addition of acetic acid did not separate the porphyrins and the brown pigment. There was a trace of ether-soluble porphyrin, which was not further purified. Precipitation by Garrod's method with calcium hydroxide brought down most of the pigment, but covering with sulfuric acid-methyl alcohol and centrifugation caused the porphyrin to come out, leaving the brown pigment behind.

The porphyrin was esterified in the acid alcohol, taken into chloroform and purified in the usual way. After several recrystallizations in chloroform the maxima for the absorption spectrum, measured in a spectrophotometer, were I, 626, II, 578, III, 538, IV, 502 millimicrons¹⁹. The crystals were sent to Prof. Hans Fischer, and his colleague Dr. Libowitzky reported:

"The 6 mg. of porphyrin ester showed fine bent recrystallized needles. The melting point was from 275 to 278 C., after sintering at 261 C. The mother liquor clearly contained coproporphyrin. The entire amount was heated with 1 per cent hydrochloric acid to 190 C. in a closed vessel for three hours, whereby the ester was saponified and decarboxylated. The resulting coproporphyrin was esterified after purification by the ether-hydrochloric acid method, and the ester crystallized. The crystals obtained sufficed for determination of the melting point at 241 to 242 C. Therefore, copro- I ester, or originally uro- I ester, was present, which is surprising in view of the clinical history. According to Waldenstrom, uroporphyrin III, which is typical of acute porphyria, was to have been expected."

The first filtrate of urine mentioned was then subjected to chromatographic analysis according to the method of Waldenstrom,^{2c} the purest aluminum oxide powder being used, with a 1,000 cc. cylindric separatory funnel holding the column of powder. The substances obtained by elutions with 20 per cent acetic acid, glacial acetic acid, distilled water and 12 per cent ammonium hydroxide were separately collected. The first of these was not further studied. Elution with glacial acetic acid yielded, in addition to a large amount of dark brown pigment (urofusin), a quantity of metal-porphyrin complex with the following absorption spectrum in glacial acetic acid: I, 565 to 550 (maximum, 557) millimicrons, II, 548 to 525 (maximum, 538) millimicrons. Elution with distilled water also brought down some metal complex.

Elution with ammonium hydroxide yielded a dark red solution rich in porphyrins. It was evaporated to about one-fifth its original volume, acetic acid was added and repeated extraction with ether was carried out. There was very little ether-soluble porphyrin, and this was not further purified. The aqueous phase was then adsorbed on a column of talc, which had been recommended by Waldenstrom^{2c} as being superior to aluminum oxide for final purification of porphyrins by chromatographic analysis.

¹⁹ The spectrophotometer manufactured by Bausch & Lomb Optical Company, Rochester, N. Y., was used.

The pigment remained limited to the upper half of the column, rendering it a pure red. The brown pigment with which it had been associated passed through, being completely removed by elution with glacial acetic acid. Some metal complex was also found in the glacial acetic acid.

The solution obtained from the talc by elution with ammonium hydroxide was a bright cherry red and showed the following spectrum: I, 570 millimicrons, shadow to 565 to 555 (maximum, 560) millimicrons, II, 540 to 525 (maximum, 530) millimicrons (order of intensity of bands I, II). After addition of acetic acid the following spectrum was obtained: I, 575 to 565 (maximum, 570) millimicrons, II, 540 to 530 (maximum, 535) millimicrons (order of intensity, I, II). With 25 per cent hydrochloric acid the following spectrum was obtained: I, very weak, about 585 millimicrons, II, fine and weak, 552 millimicrons (order of intensity II, I). After extraction from 25 per cent hydrochloric acid with amyl alcohol, the following absorption was noted in the alcohol: I, 565 millimicrons, II, about 535 to 525 millimicrons (order of intensity I, II). This pigment was removed from amyl alcohol by tenth-normal potassium bicarbonate, in which the absorption was: I, 565 millimicrons, II, 535 to 530 millimicrons.

The addition of acid led to the precipitation of the pigment, which was filtered off, taken into 5 per cent ammonium hydroxide and reprecipitated. This time an astonishing fact was noted. The greater part of the pigment, a metal complex, remained in solution at p_H 3.4. This was sent to Dr. C. J. Watson for study. The precipitate was insoluble in pyridine, but on addition of water it formed a bright red solution with the following absorption: I, 595 to 575 (maximum, 580) millimicrons, II, 550 to 530 (maximum, 538) millimicrons. Within a few minutes this had changed, band I moving to a maximum at 592 millimicrons, band II disappearing and a new band coming in at 630 millimicrons. With this, another appeared at about 500 to 490 millimicrons. On addition of a few drops of dilute ammonium hydroxide the absorption was: I, very fine, 605 millimicrons, II, 585 to 575 millimicrons, followed by diffuse absorption in the green and extinction at about 500 millimicrons. On addition of acetic acid the absorption changed to: I, 630 millimicrons, II, asymmetrical, 605 to 590 (maximum, 600) millimicrons (order of intensity II, I). After twenty-four hours a precipitate formed and was filtered off. A test portion of this precipitate dissolved in pyridine showed the following absorption: I, about 610 millimicrons, II, very intense, asymmetrical, 580 to 560 (maximum, 565) millimicrons, III, intense, 535 to 525 (maximum, 530) millimicrons, IV, 505 to 480 (maximum, 490) millimicrons.

The remainder of the precipitate was covered with 2 per cent sulfuric acid-methyl alcohol and set aside to esterify. The violet solution was filtered off, leaving a red residue on the filter paper. The violet solution was added to a small volume of chloroform, water was then added and the chloroform solution of the pigment was washed with dilute sodium bicarbonate and evaporated to dryness in vacuo. Redissolved in chloroform it showed the following absorption: I, 625, II, 570, III, 535, IV, 500 millimicrons (spectrophotometric maxima). These are identical with those of uroporphyrin²⁰. The previously mentioned insoluble red residue was dissolved in chloroform and washed according to the method described. It then had the following spectrum in chloroform: I, 585 millimicrons, shadow to 570 to 555 (maximum, 562) millimicrons, II, 535 to 518 (maximum, 530) millimicrons (order of intensity I, II).

20 Maurer, H. Tierische Farbstoffe und synthetische Porphyrine, in Abderhalden, E. Biochemisches Handlexikon, Berlin, Urban & Schwarzenberg, 1933, vol. 7, pp. 605-766.

The evidence thus far pointed to the occurrence of uroporphyrin I, together with a larger amount of metal-porphyrin complexes of the type of turacin²¹ The metal or metals in these complexes were not identified With this was excreted one or more chromogens, giving rise to the red-brown of the urine One of these chromogens gave a positive reaction to aldehyde (Ehrlich) Little coproporphyrin could be found either in urine or in feces The porphyrins did not accumulate in the blood stream but were easily excreted There was evidence of hepatic damage, apparently involving more of the excretory function than of the metabolic There was evidence of slight macrocytic erythropoiesis

It was thought desirable to repeat this study during the patient's second attack wherefore 4 liters of urine was collected for study²² This time it was found that uroporphyrin I (melting point, 292 C, uncorrected) was excreted in considerably greater amount than were metal complexes After the publication of Waldenstrom's monograph⁶ the uroporphyrin from the mother liquors of the uroporphyrin I crystallizations was reexamined It was then found that a considerable amount of uroporphyrin could be separated which had a noticeable solubility in absolute methyl alcohol Comparison of two solutions of uroporphyrin, the one containing pure uroporphyrin I from Hans Fischer and the other from the mother liquors previously mentioned, revealed a marked difference in the solubility of the porphyrins on addition of methyl alcohol That of the pure uroporphyrin I was negligible, the other left a bright red solution Evaporation of this solution to small volume and cooling to -10 F gave a small yield of fine crystals arranged in burrs The yield was too small for a determination of the melting point, but the spectrum in chloroform was that of uroporphyrin

Further studies of urofuscin were made and agreed in essence with the former

COMMENT

It is evident that the acute attacks from which the patient suffered were exacerbations of a chronic condition A review of the literature reveals this to be almost invariably so In this connection Waldenstrom's⁶ monograph is most instructive One of his patients has had porphyria for more than a quarter of a century without experiencing an acute attack^{2b}

Aside from the familial occurrence in Sweden, which Waldenstrom's data indicated to be transmitted as a dominant mendelian characteristic, nine families, including that of the present patient, have been known to have more than one member with porphyria²³

21 Fischer, H, and Hilger, J Zur Kenntnis der natürlichen Porphyrine VIII Ueber das Vorkommen von Uroporphyrin (als Kupfersalz, Turacin) in den Turakusvögeln und den Nachweis von Koproporphyrin in der Hefe, *Ztschr f physiol Chem* **138** 49, 1924

22 This part of the work was assisted by a grant from the Committee on Scientific Research of the American Medical Association

23 van Berckel, G J J Porphyreën en Porphyrinen Geneesk bl u klin en lab v d prakt **25** 1, 1926 Larjanko, J Klinische-pathologische Untersuchungen über die Porphyria idiopathica abdominalis, *Acta Soc med fenn duodecim* **21**·1, 1935 Mason, V R Personal communication to the author Micheli, F

According to Waldenstrom,⁶ the criterion for the diagnosis of porphyria is the demonstration of uroporphyrin in the urine. In congenital porphyria, with dermal manifestations, uroporphyrin I is the main type excreted, with a small amount of uroporphyrin III.⁸ In acute porphyria type III preponderates. In addition there is excreted in cases of acute porphyria a substance which gives a positive reaction to aldehyde (Ehrlich). Waldenstrom⁶ distinguished this from uro-fuscinogen, which gives a brownish pigment, stating that the aldehyde reactor yields a red substance on oxidation. Further, he identified this chromogen with a substance which gives a positive diazo reaction (Ehrlich). There appears to be still another characteristic of acute porphyria—the excretion of metal complexes. Waldenstrom²⁰ mentioned it as occurring in the eluate of pigment from aluminum oxide by distilled water. It occurred in the present case. It has been noted in the porphyria of the fox squirrel.^{7a} Whether it might be an artefact due to contamination by metals and subsequent complex formation must remain an open question at present.

The significance of uroporphyrin is unknown. To me it seems plausible that uroporphyrins are formed in the bone marrow from pyromethenes brought from the liver by the blood stream.²⁴ It is possible that the coproporphyrins arise by decarboxylation of the uroporphyrins, for Dobriner and his associates³ have shown that coproporphyrin excretion may be taken as an index of bone marrow activity. It is also possible that protoporphyrin is a product of still further decarboxylation of uroporphyrin.

Therapeutically there is relatively little that can be done for the patient with porphyria. Liver therapy is of little or no avail.²⁵ Indeed, Dobriner²⁶ has shown that although excretion of porphyrin in acute and congenital porphyria may be diminished by liver therapy, the excre-

and Dominici, G. Ueber zwei Falle von familiarer Porphyrie mit letalem Ausgang, *Deutsches Arch f klin Med* **171** 154, 1931. Barker, L. F., and Estes, W. L. Family Hematoporphyrinuria and Its Association with Chronic Gastro-Intestinal Dilatation, Peculiar Fits and Acute Polyneuritis, *J A M A* **59** 718 (Aug 31) 1912. Ehrenberg, L. Zur Kasuistik der mit Landryscher Lahmung einhergehenden Porphyrinuria, *Klin Wchnschr* **2** 1508 (Aug 6) 1923. Scholberg, H. A. An Undescribed Purple Pigment in the Urine, *Tr Path Soc London* **53** 279, 1902. Maugeri, S. Porfirinuria familiare e porfiria idiopatica, *Riforma med* **52** 919, 1936.

²⁴ Borst, M., and Konigsdorffer, H. Untersuchungen uber Porphyrie mit besonderer Berucksichtigung der Porphyria congenita, Leipzig, S. Hirzel, 1929. Dobriner and Rhoads.^{3d}

²⁵ Waldenstrom.⁶ Turner and Obermayer.^{7b}

²⁶ Dobriner, K. Discussion at the Pediatric Session of the Southern Medical Society, Baltimore, Nov 17, 1936, after presentation of two patients with porphyria by Dr. Harriet M. Guild. A report of these cases has not yet been published.

tion of uroporphyrin is not stopped. During the acute attack calcium therapy is effective for the relief of pain,²⁷ but whether it affects the ultimate outcome of an attack is uncertain.

SUMMARY

A patient with acute idiopathic porphyria with symptoms of lead poisoning excreted large amounts of a red-brown pigment complex called urofusin. With this there were excreted also a small amount of uroporphyrin I and probably uroporphyrin III, together with considerable amounts of an unidentified metal complex. In the interval between attacks there was a larger amount of metal complex excreted than of porphyrin, during an attack this relation was reversed.

The hypertension noted during an attack disappeared as the symptoms abated.

- During the interval between symptoms there were persistent excretion of urofusin and evidence of hepatic disease.

The evidence points to the conclusion that acute idiopathic porphyria is actually a chronic metabolic disturbance. The familial occurrence of the condition substantiates the thesis that acute idiopathic porphyria is an inherited inborn error of metabolism.

Chemical studies of the blood and urine are reported which suggest the presence of hepatic damage, with bilirubinemia but little urobilinogenuria. The strong positive reaction of the urine to aldehyde (Ehrlich) was shown to be due to a chromogen, probably not urobilinogen.

It is suggested that uroporphyrins are formed in the bone marrow as the primary porphyrin complex, from which the coproporphyrins and protoporphyrin arise by decarboxylation.

CONCLUSIONS

Acute idiopathic porphyria may be associated with excretion of uroporphyrin I in excess of uroporphyrin III.

Excretion of metal-porphyrin complexes appears to be characteristic of acute idiopathic porphyria.

Most of the color of the urine in acute idiopathic porphyria is usually due to the presence of pigments which have been called urofusin.

Acute idiopathic porphyria is a familial disease, probably inherited as a dominant mendelian characteristic.

The acute manifestations are alleviated by intravenous calcium therapy.

²⁷ Hoergurber, W., and Fink, H. Ueber Porphyrine bei klinischer Porphyrrie, *Ztschr. f. physiol. Chem.* **236** 136, 1935. Waldenstrom,^{2a} Fischer and Libowitzky.⁸

GASTRIC SECRETION IN MAN

OBSERVATIONS ON THE EFFECTS OF REPEATED INJECTIONS OF
HISTAMINE AND ON TRANSIENT ACHLORHYDRIA

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The following report is based on studies carried out on a trained subject for four and a half years. The subject was originally selected to serve as the source of gastric juice for patients with pernicious anemia. Because of the fact that he was receiving repeated injections of histamine, we decided to study his gastric secretion. At first attention was paid only to the volume and the acidity, later, determinations of pepsin and chloride were included.

F F, aged 49 years, a foreman of a railroad gang, entered the Cincinnati General Hospital, in February 1931, with paralysis of the extremities following ingestion of adulterated Jamaica ginger. His past history was unimportant except for chronic alcoholism. He had been surprisingly free from digestive disturbances. The general physical examination revealed only evidence of peripheral neuritis and of some involvement of the pyramidal tracts. The blood count, urinalysis and stool analysis gave normal results. The Wassermann reaction of the blood was negative. Roentgenograms of the gastrointestinal tract were normal. The basal metabolic rate was -16 per cent.

Soon after admission to the hospital the patient regained the full use of his upper extremities. His lower extremities, however, remained permanently damaged, so that he was unable to walk, but he was able to get about readily in a wheelchair. He was intelligent and cooperative. He was weighed twice weekly, and his blood was examined once a month.

REPEATED INJECTIONS OF HISTAMINE

Method Used—At 9 a m, after a twelve hour fast, a Rehfuess tube was swallowed, and the gastric contents were removed and examined. One-half milligram of histamine phosphate was given subcutaneously, and the injection was repeated one-half hour later. Continuous aspiration with a 50 cc syringe was practiced by the patient for two and one-half hours. The total quantities

Read before the American Society for Clinical Investigation, May 4, 1936, Atlantic City, N J

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This study was made possible by a grant from Parke, Davis & Co and through the W T Wagner & Sons Fund for the Study of Gastritis and Related Conditions

obtained during half-hour periods were examined separately¹ An emesis basin was always at hand to receive any saliva that might be secreted during the aspiration, but fortunately the quantity was insignificant Frequent control observations were made under fasting conditions for two and one-half hour periods without the injection of histamine There was generally secreted about 250 to 350 cc of gastric juice under such conditions, in contrast with an average of 350 to 500 cc after an injection of histamine Attention was always paid to the presence of bile and mucus Fortunately bile was rarely present, and the quantity of mucus was generally negligible The juice obtained was thin, clear and colorless The titratable acidity was determined by the standard method, Topfer's reagent and phenolphthalein being used as indicators and titration being carried out with tenth-normal sodium hydroxide The chloride content was estimated by the method of Van Slyke and Sendroy The pepsin content was measured by the Mett's tube method

Results—Up to May 1, 1936, the patient had had 433 aspirations, carried out as outlined, and had received 799 injections of 0.5 mg of histamine² He still experienced the same effects noticed after the initial injections There was a general tingling sensation accompanied with a feeling of warmth, which started about two minutes after the injection and lasted about four to six minutes This was accompanied with a slight throbbing in the head and followed by slight transient headache There was general flushing of the skin, and exceptionally an urticarial wheal developed at the site of injection There was a slight increase in pulse rate, with no change in the arterial blood pressure

The patient apparently incurred no harm from the injections By May 1936 he was 30 pounds (13.6 Kg) heavier than he was on admission to the hospital Monthly blood counts remained within normal limits Repeated determinations of the chloride content of the blood gave normal results Repeated roentgenographic examinations of the gastrointestinal tract revealed normal rugae and no change in motor function Five gastroscopic examinations were made 4 by Dr Samuel Igler with the rigid tube and 1 by Dr Rudolph Schindler with the flexible gastroscope The findings were not noteworthy except for those of mild superficial gastritis

TRANSIENT ACHLORHYDRIA

A Initial Phase (Absolute Achlorhydria)—In the first few months of study the average total volumes obtained during two and a half hour periods following the injection of histamine ranged between 170 cc (December 1931, 8 determinations) and 250 cc (March 1932, 8

1 On some occasions either 1 or 2 injections of histamine were given, and the gastric juice was collected during ten minute periods

2 Between January 1935 and January 1936, 104 injections were given without subsequent aspirations

determinations) Later these increased to between 435 cc (December 1932, 17 determinations) and 568 cc (December 1933, 10 determinations) In February 1934 the average volume after the injection of histamine had decreased to 332 cc (5 determinations), in April 1934 the average volume was 365 cc (6 determinations) The range of acidity during a corresponding period is given in chart 1

Aspirations were not performed between May 1 and July 23, 1934, during this period no histamine was given, as studies were being made of the patient's duodenal contents By July 24 there had developed a histamine-refractory achlorhydria associated with a disappearance of pepsin and a decrease in volume of gastric juice to 123 cc Achlorhydria was also present on July 28 (volume, 131 cc), August 15 (volume, 110 cc) and September 14 (volume, 178 cc), as shown in chart 2

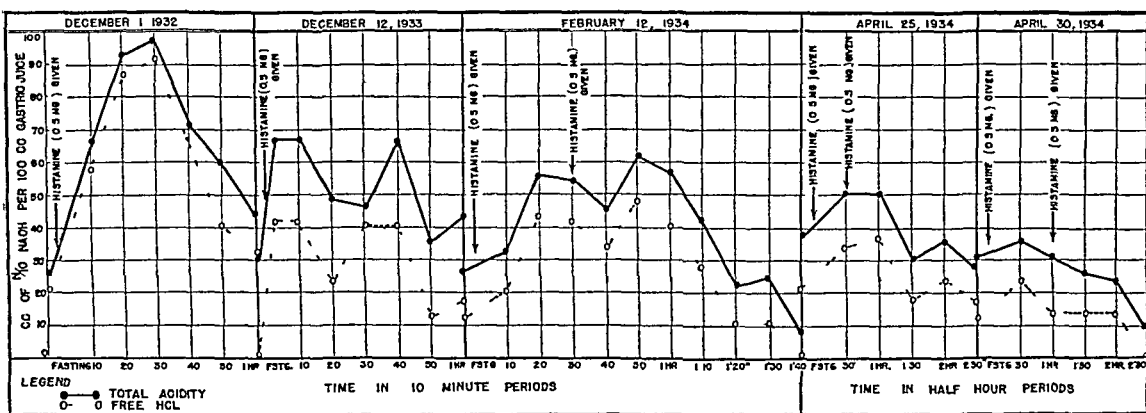


Chart 1—Curves showing the acidity after the injection of histamine (patient F F)

None of the usual causes of achlorhydria, such as infection, dietary deficiency, mental or emotional strain or a bout of alcoholism, could be held accountable

As the patient had received a total of 379 injections of histamine, the question arose as to whether or not the achlorhydria was an exhaustion effect produced by histamine On October 12, after an injection of histamine, the gastric juice showed a return of free acidity (maximum, 14) and on November 9 a maximum acidity of 15 From January to June 1935, inclusive, the patient was given 221 injections of histamine in the face of which there was a gradual rise in the gastric acidity, which reached normal limits in July (chart 3) From July 1935 to January 1936, inclusive, a total of 167 injections were given, the acidity remaining normal The gradual increase in acidity and the persistence of normal values in spite of repeated injections of histamine (total, 388) would exclude an exhaustion effect

B Second Phase (Relative Achlorhydria)—In connection with a study of the influence of the endocrine glands on gastric secretion, the patient was given subcutaneously a total of 60,000 iat units of estrogenic substance³ between Dec 16 and 21, 1935, and an additional 120,000 units between Jan 1 and 12, 1936, inclusive, in doses of 10,000 units daily, receiving in all a total of 180,000 units. During this period gastric analyses were made almost daily both with and without the injection of histamine. On January 31 the volume of gastric juice after an injection of histamine was 425 cc., and the acidity was normal. On February 3 achlorhydria was encountered in all but the second half-

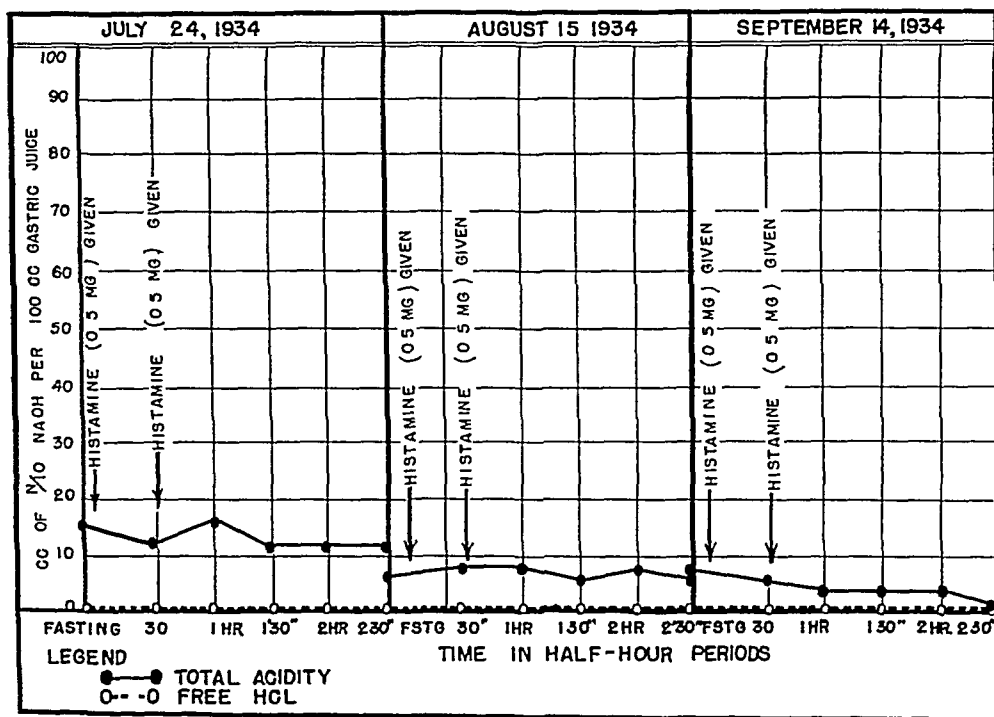


Chart 2—Curves showing the acidity after the injection of histamine (first phase of achlorhydria, patient F F)

hour specimen, which showed a free acidity of only 7 (chart 4). The total volume of juice secreted during the two and one-half hour period was 375 cc., showing little decrease in contrast with the first phase of achlorhydria, in which the volume fell decidedly and in which, of course, the achlorhydria was absolute. There was no recognizable increase in the mucus content of the juice. On February 4 and 5 free hydrochloric acid was again present only in the second half-hour period after the injection of histamine, with values of 3 and 12, respectively. Daily aspiration conducted without the use of histamine between February 6 and 16 and between February 25 and March 2,

³ The preparation used was theelin.

inclusive, revealed achlorhydria in all specimens, with an average total volume of 292 cc. On February 17 and 24 the second half-hour specimen after an injection of histamine contained a free acidity of 19 and 16, respectively, the remaining specimens containing no free acid. On March 5 the specimen obtained during fasting contained a trace of

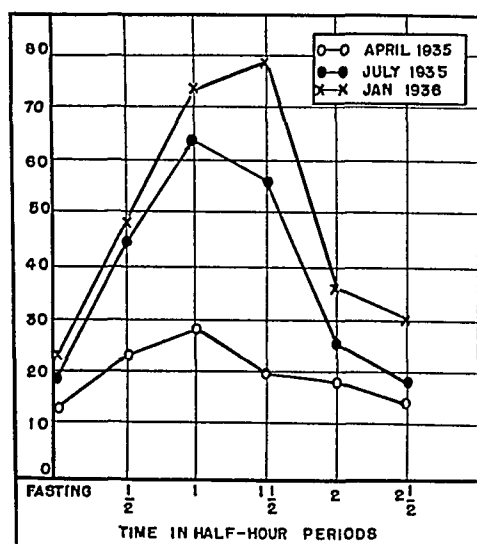


Chart 3—Curves showing the average acidity after the administration of histamine

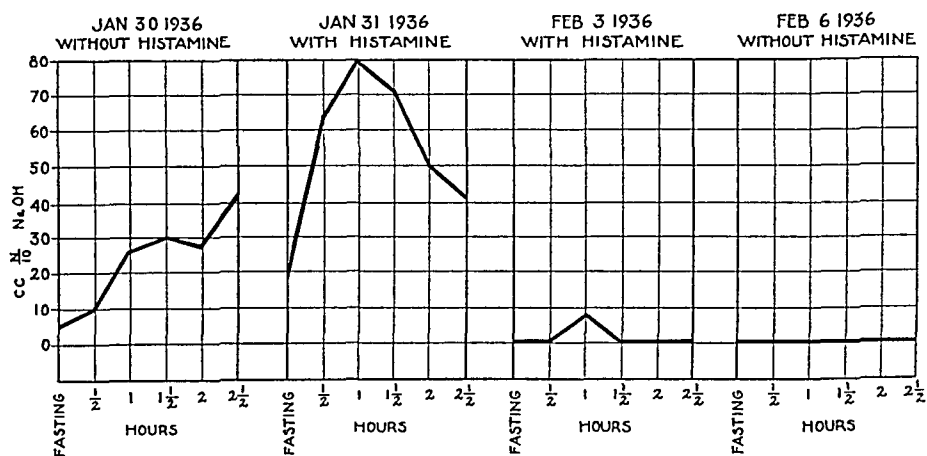


Chart 4—Curves showing the change from normal secretion to relative achlorhydria

free hydrochloric acid, and the fourth half-hour specimen, obtained without the use of histamine, showed a free acidity of 3. On March 11, after an injection of histamine, free acid was present in all but the fifth half-hour specimen, with a maximum value of 22. From then until May 1, 15 aspirations done without the injection of histamine showed

achlorhydria in 3 and free acid in almost all fractions in the remaining 12 specimens, while those done after the injection of histamine showed the presence of free hydrochloric acid in at least 4 specimens on 5 of 6 occasions. There was thus a gradual increase in the secretion of hydrochloric acid (chart 5).⁴

The relative achlorhydria was accompanied with an almost complete disappearance of pepsin. Again, none of the recognized causes of achlorhydria could be discovered. The estrogenic substance was suspected, and accordingly injections of it were given to three (male) patients, with no appreciable effect on gastric acidity.⁵

During each period of depressed secretion of acid the patient complained of epigastric distress immediately after meals, accompanied

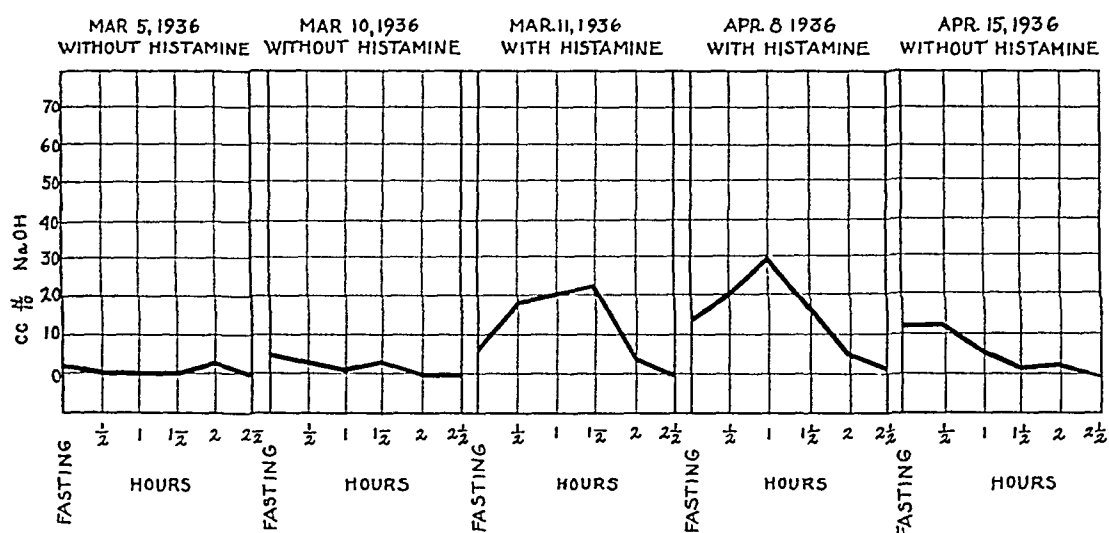


Chart 5—Curves showing the gradual increase in free hydrochloric acid

with considerable belching. In addition, there developed diarrhea, with an average of four to five loose, watery movements per day. Fatigability and lack of ambition were prominent. The administration of 30 drops of hydrochloric acid in a glass of water with meals was followed by partial relief.

Interestingly, gastroscopic examination revealed no gross change in the appearance of the gastric mucosa with the onset of achlorhydria. Mild superficial gastritis was encountered, a finding which had been noted four times previously.

During the second achlorhydric phase it was decided to determine whether or not the so-called intrinsic antianemic factor was still present, as it had been previously found to be. Accordingly Castle's original

⁴ Normal values were eventually reached.

⁵ Injections of estrogenic substance were given our subject in May 1937 without effect.

experiment was repeated, and two (controlled) patients with pernicious anemia were given 200 Gm of beef muscle incubated with 250 cc of gastric juice daily for ten days. The juice was obtained without histamine and was devoid of free hydrochloric acid. It was kept on ice until ready for use. In both instances there developed reticulocytosis, followed by an increase in the hemoglobin and red blood cell values and accompanied with marked clinical improvement, proving that the antianemic substance had not disappeared.

SUMMARY AND CONCLUSIONS

Repeated (799) subcutaneous injections of histamine phosphate in 0.5 mg doses were given to a patient over a period of four and one-half years, with no apparent harm and without overfatigue of the mechanism of hydrochloric acid secretion.

The human stomach may temporarily lose its ability or may exhibit a marked decrease in its ability to secrete free hydrochloric acid for no definitely known reason and with no change in the mucous membrane detectable on gastrosopic examination.

Absence of pepsin may be associated with the temporary disappearance of free hydrochloric acid.

The so-called intrinsic antianemic substance may still be present during a period of (relative) achlorhydria.

CALCIFIC AORTIC STENOSIS

A CLINICAL AND ELECTROCARDIOGRAPHIC STUDY

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PATHOLOGIC PICTURE

After Monckeberg's first description of the pathologic picture of calcific aortic stenosis, in 1904, this lesion for years was reported only rarely and was recognized only at postmortem examination. In recent years, however, clinical and roentgenologic studies have allowed its recognition during life without difficulty.

Various authors (Monckeberg, Ribbert, Maigolis, Ziellessen and Baines, Giese, Martens and others) have investigated the underlying pathologic condition, and their findings will be reviewed here as they are necessary for a better understanding of the clinical and roentgenographic aspects.

The involvement affects the aortic ring, primarily at the roots of the valves. In the first stage of the disease only the outer layer at the site of the sinus of Valsalva is affected. Calcification then extends into the leaflets or into one of the commissures, bulges into the sinuses of the valves or forms radiating or circular buckles within the valves themselves. Deposits of lime salt may fill up the sinuses completely. From there the condition may progress into the ventricles, producing spurlike formations under the endocardium. Such formations usually extend from the posterior aortic valve as far as the large leaflet of the mitral valve. An extension from these valves to the pars membranacea septi or to the muscular portions of the septum is less frequent. Calcification of the aortic valves may occur in combination with calcification of the annulus fibrosus or may be entirely isolated. The valves themselves are thickened, have an irregular surface and are fused at the commissures. The places of fusion may shrink considerably and in so doing usually cause stenosis of the valves.

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According to Libman, the presence and the amount of arteriosclerosis and calcification in the aorta depend on whether or not the lesions in the valves precede the involvement of the aorta by any considerable period. If stenosis occurs before lesions of any consequence have developed in the wall of the aorta, the latter may be thin and smooth.

ETIOLOGY

The etiology of calcific aortic stenosis is still unknown. In only 20 per cent of the seventy-seven cases reported was there a definite history of rheumatic fever. The solitary occurrence of the lesion, i. e., the absence of involvement of the mitral valve, the lack of appreciable thickening or shortening of the chordae tendineae, the massive deposit of calcium, the predominant occurrence of the condition in older men and the nonpresence of recent or old Aschoff bodies in the myocardium—all speak against a rheumatic etiology. As has been indicated, the early changes in Monckeberg's sclerosis fail to disclose a primary inflammatory basis, and there are no marked arteriosclerotic changes elsewhere. The coronary arteries may reveal some degree of sclerosis in older persons, but the degree of disease of the coronary arteries is not greater than one would expect to encounter in a group of normal persons of the same age. Furthermore, the occasional occurrence of calcific aortic stenosis among younger persons also speaks against an arteriosclerotic basis.

In this discussion we are excluding those cases of calcification encountered in the course of the so-called healed subacute bacterial endocarditis described by Libman and the not infrequent examples of calcification observed in long-standing rheumatic or syphilitic heart disease.

The degenerative and infiltrative processes speak for an individual predisposition toward their formation which may exist in certain persons. While the possibility that the lesion represents the healed stage of an inflammation still remains open, its exact etiology still remains problematic. The most likely conclusion, based on our present findings, is that the disease is primarily degenerative in nature, its occurrence and extent depend on an individual predisposition toward collagen involution and lipid and calcium deposition.

CLINICAL SIGNS

In recent American literature Christian (1931), in a postmortem study of twenty-one cases, first emphasized the clinical entity of calcific aortic stenosis, its predominant occurrence in middle-aged and elderly subjects and its slow course, resulting in relatively late cardiac failure.

and occasionally in sudden death. The important classic diagnostic physical signs are a long loud rough systolic murmur transmitted to the vessels of the neck, the systolic thrill over the aortic area, frequently best felt with the patient in the knee-chest position, the absence or diminution of the intensity of the aortic second sound, especially in the vessels of the neck, and considerable cardiac hypertrophy. The soft blowing diastolic murmur of aortic insufficiency is frequently, though not invariably, heard. Usually a softer systolic murmur is heard over the mitral area and is probably due to a relative mitral insufficiency. A faint wavy or rumbling diastolic murmur is also occasionally heard at the apex (Austin Flint murmur). In cases in which there is no associated marked aortic insufficiency or hypertension the pulse is characteristically small and anacrotic or bisferious, and the pulse pressure is normal or diminished. Occasionally the classic physical signs of aortic stenosis may not be present, leaving only the physical signs of aortic regurgitation obvious. This picture is present in the particular group of cases in which the diagnosis is frequently overlooked.

The presence of aortic regurgitation in the absence of any signs of mitral stenosis, when syphilitic heart disease can be excluded, should suggest the possibility of calcific disease of the aortic valves. In cases in which the initial insult to the valves is slight, only indistinctive clinical manifestations are produced, and heart failure consequent to the developing stenosis and subsequent death occur late. These meager clinical manifestations, without cardiac symptoms until late in the disease, and the constant presence of aortic regurgitation are strongly suggestive of calcific aortic valvulitis.

FLUOROSCOPY AND AIMED ROENTGENOGRAPHY

The number of calcifications of the cardiac valves recognized roentgenographically *in vivo* has increased considerably in the last four years.

Simmonds (1908) first made a roentgenographic study of calcifications of the heart in five cases at necropsy. Klason (1921) first diagnosed calcified annulus fibrosus *in vivo*, Fleischner (1925) and Saul (1932) reported similar cases. Christian (1931) first emphasized the potentialities of the roentgenographic demonstration of cardiac calcifications *in vivo*, and his collaborator, Sosman, first reported such a case. Sosman and Wosika (1933) were able to report twenty cases of calcific aortic stenosis and nineteen cases of calcification of the mitral valve observed roentgenographically before death.

Further observations of roentgenographically diagnosed intracardiac calcifications were published by Parade and Kuehlman (1933), who

saw five patients, one with calcific aortic stenosis Sparks and Evans (1935) reported one case of calcification of the aortic valves, Bishop and Roesler (1934), three cases, all with autopsies, Blackford (1936), one case, Cooley (1936), one case, Willius (1935), sixteen cases of calcific aortic stenosis, and Kommerell (1936), ten cases in which there were four calcified aortic valves

The proper use of roentgenoscopy and aimed roentgenography was the contributing factor in making the recognition of calcified aortic stenosis possible when clinical symptoms were rather indefinite With aimed roentgenography the calcified depositions are localized fluoroscopically in the best view obtainable and with a special device, the serialograph, immediately roentgenographed, with an exposure of 0.05 second (75 kilovolts and 100 milliamperes)

The calcified valves show up under fluoroscopy as small dense shadows, rapidly moving or dancing up and down They cannot be projected outside the cardiac shadow and are not affected by deep inspiration They move more rapidly than the pulsating left cardiac border They are seen in the median line or a little to the right of it in the lowest third of the cardiac area They are best observed at the right oblique angle, as the movement is most marked in this view The observer's eyes must be well adapted, and the smallest diaphragm must be used in order to obtain sharp visualization of the fine details Experienced observers are often able to localize these calcifications Mitral calcifications are situated more medially and show marked rapid pulsatory motion, whereas the aortic deposits of calcium show less extensive and more dancing movement The calcifications of the annulus fibrosus have ring forms and move relatively little

Little difficulty is experienced in differentiating the calcified valves from other calcifications Occasionally they may be confused with calcified thrombi Calcified coronary arteries are recognized only in exceptional cases

Myocardial calcifications are rare Smaller pericardial calcifications may, if the patient is turned, be projected on the cardiac margin and thus easily differentiated from endocardial calcifications Hilal calcifications can easily be excluded

REPORT OF CASES

We present here fourteen cases of calcific aortic stenosis The patients were observed at Bellevue Hospital during the last seven years, with nine autopsies Five of the patients (cases 1 to 4 and 14) are still living and under observation It is only for the latter group, in the last few years, that we have applied systematically the roentgenographic

procedure, with correspondingly gratifying results. Except in these five cases, the correct diagnosis was not made until after death (table).

Four of the nine patients studied at autopsy had the physical findings of aortic insufficiency and suffered cardiac pain. These same four displayed the typical electrocardiographic changes of myocardial damage associated with disease of the coronary arteries. Yet all the necropsies revealed calcific aortic stenosis, with patent coronary arteries showing minimal sclerosis. All the patients who have not yet come to autopsy have revealed the physical findings of aortic insufficiency and have suffered cardiac pain. Four of these five patients have shown electrocardiographic evidence of myocardial damage. Roentgenographic examination has revealed calcific depositions in the aortic valves of all five patients. Syphilis and bacterial endocarditis were not present in any of the fourteen cases.

From the evidence just presented, it may be seen that when the physical signs of aortic insufficiency are accompanied with the electrocardiographic findings of myocardial damage and when syphilitic disease and acute and subacute bacterial endocarditis are absent, a diagnosis of calcific aortic stenosis is indicated. Roentgenographic examination will confirm or contradict this impression.

CASE 1—J. M., a man aged 43, had had recurrent cardiac pain radiating down the left arm and shortness of breath on exertion for ten years. He had been admitted to the hospital three times because of cardiac pain and addiction to phenobarbital. There was no history of rheumatism. He complained of precordial pain caused by effort or excitement. There was no history of congestive failure.

Physical examination revealed a fairly well developed man. The pupils were equal and reacted to light and in accommodation. There was no congestion of the veins of the neck. The lungs were resonant throughout. Examination of the heart showed that the point of maximal impulse was in the sixth intercostal space 11.5 cm. from the midsternal line. A faint systolic thrill was noted over the aortic area. The second aortic sound was absent over the aortic area and the carotid vessels. The first apical sound was loud and accentuated, with a soft short diastolic murmur over the left sternal border. The blood pressure was 124 systolic and 65 diastolic. There was a Corrigan pulse, no capillary pulse was noted. The liver and spleen were not palpable. No pretibial edema was present. The Wassermann reaction was negative. The basal metabolic rate was -3 per cent. The urine was normal.

An electrocardiogram taken on April 10, 1935, showed normal sinus rhythm, with a rate of 80 per minute. The PR interval was 0.16 second and the QRS interval 0.8 second. There was no deviation of the electrical axis.

The electrocardiogram showed that QRS_1 was split and of low amplitude. The T wave was of the inverted seagull type in lead I and was inverted in all leads. The form of the T wave and its low amplitude suggested myocardial damage. At present the patient shows practically the same electrocardiographic picture as when admitted to the hospital. The initial and final ventricular complexes are characteristic of myocardial changes associated with recent closure of the coronary vessels.

Case	Sex	Age	Rough Loud Aortic Systolic Murmur	Aortic Systolic Thrill	Soft Blowing Diastolic Murmur of Aortic Insufficiency	Absent or Diminished Aortic Second Sound	Marked Cardiac Hypertrophy	Small Soft Anacrotic Pulse	Röntgen Findings	Electrocardiographic Findings	Slow Development of Congestive Failure	Dyspnea and Edema	Cardiac Pain
1	M	43	+	+	+	+	+	-	+	Inverted seagull T ₁ , cove plane T ₂ and T ₃	-	+	+
2	M	37	-	-	+	-	+	+	-	Normal sinus rhythm no deviation upright T wave in all leads	-	+	+
3	M	70	-	+	-	+	+	-	-	Left bundle branch block, inverted T ₁ upright T ₂ , opposite main deflection	+	-	-
4	M	60	+	+	+	+	+	-	-	Left bundle branch block QRS notched and slurred in all leads	-	-	+
5	M	50	+	+	+	+	+	+	-	Inverted T ₁ and T ₂ , slurred QRS, later inverted T ₁ , diphasic T ₂ and T ₃	+	+	+
6	M	63	+	+	+	+	+	-	-	Inverted T ₁ and T ₂	+	+	+
7	M	39	+	+	-	+	-	-	-	Diphasic T ₁ , T ₂ and T ₃ , intraventricular block	-	+	+
8	M	49	-	-	+	-	+	-	-	Inverted T ₁ and T ₂ , diphasic T ₂	+	+	+
9	M	54	-	+	+	+	+	+	-		+	+	+
10	M	47	-		+		+	-	-		+	+	+
11	M	68	+		+	-	-	-	-		-	-	-
12	F	74	+		+	-	-	-	-		-	-	-
13	M	60	-		+	-	-	-	-		-	-	-
14	M	68	+		+	+	+	+	+	Normal sinus rhythm left axis deviation	+	+	-

Syncope	Death Due to Cardiac Failure	Sudden Death	Autemortem Diagnosis	Arteriosclerotic Aortic Insufficiency	Mitral Stenosis	Necropsy Observations	Comment
-	-	-	Arteriosclerotic heart disease	+	-		
-	-	-	Arteriosclerotic heart disease	+	-		
-	-	-	Arteriosclerotic heart disease	+	-		
-	-	-	Arteriosclerotic heart disease	-	-		
-	-	-	Arteriosclerotic heart disease	-	-	Chronic aortic calcific valvulitis, aortic cusps fused, thickened, stiffened and distorted by calcareous deposits	Coronary arteries entirely free from sclerosis, diagnosis acute coronary thrombosis with left pleural effusion
-	-	-	Arteriosclerotic heart disease	-	-	Aortic valves totally calcified, calcification covered by intima for most part, but eroded in some areas, displaying thrombi of recent origin, calcification extended on aortic surface along commissures	Coronary arteries patent throughout, showed minimal sclerosis
+	-	+	Arteriosclerotic heart disease	-	-	Calcified aortic valvulitis superimposed on congenital bicuspid aortic valve	Coronary arteries well preserved and patent
-	-	-	Arteriosclerotic heart disease	-	-	Aortic valves showed extensive deposits of calcareous granules	Orifices of coronary arteries shut off to large extent by atheromatous process
-	+	-	Calcified aortic valvulitis	-	-	Aortic cusps calcified	Coronary arteries well preserved
-	-	-	Rheumatic heart disease, mitral stenosis, aortic stenosis	-	+	Mitral valve thickened and cusps fused, aortic valves replaced by calcareous deposits which narrowed the orifices to 4 mm , soft vegetations superimposed on calcified areas	Coronary arteries patent throughout
+	-	+	Arteriosclerotic heart disease	-	-	Atherosclerosis with calcification of mitral and aortic valves	Carcinoma of esophagus with metastasis in liver
-	-	-	Arteriosclerotic heart disease	-	-	Aortic valves thickened, calcareous ring at base of valves	Coronary arteries entirely free from sclerosis, fracture of neck of femur
-	-	-	Arteriosclerotic heart disease	-	-	Aortic cusps showed small sclerotic and calcified plaques	Coronary arteries sclerotic, lumens patent, abscess of lung
-	-	-	Arteriosclerotic heart disease, essential hypertension	+	-		

Roentgen examination revealed a normal pulmonary parenchyma (fig 1) The heart was slightly enlarged The aorta was well within normal limits Roentgenoscopy revealed rapidly pulsating calcifications of the aortic cusps

The history of precordial pain radiating down the left arm, coming on after exertion and occasionally during rest, and dyspnea on effort, with electrocardiographic findings of a cove plane T wave in leads I to III for a young subject, strongly suggested myocardial infarction due to coronary closure, yet the roentgen evidence proved that this was a case of calcific aortic disease

CASE 2—J S, a man aged 37, had had precordial pain since 1922, with occasional pain down the left arm coming on after exertion and also while at rest and dyspnea on effort He slept on two pillows and always felt tired There was no rheumatic history An extragenital chancre developed in November 1936

Physical examination revealed a fairly well nourished man The pupils were equal and reacted to light and in accommodation There was no congestion of the veins of the neck The heart was enlarged to the left The point of maximal impulse was in the sixth intercostal space 11 cm from the midsternal line A



Fig 1—Roentgenographic appearance in case 1

systolic thrill was noted over the aortic area The aortic second sound was absent over the carotid and aortic areas A loud rough systolic murmur was noted over the aortic area and over the left sternal border There was a short apical systolic murmur, with a mid-diastolic murmur over the apex (Austin Flint murmur) There was a normal sinus rhythm The blood pressure was 102 systolic and 70 diastolic The liver and spleen were not felt There was no pretibial edema

The electrocardiogram showed a normal sinus rhythm There was no deviation of the electrical axis The T wave was upright in all leads

Roentgen examination revealed mitral configuration of the heart, within normal limits, and hypertrophy of the left ventricle The aorta was moderately elongated and widened, with characteristic dancing calcific depositions in the aortic cusps (fig 2)

CASE 3—R H, a man aged 76, had had symptoms of cardiac pain on exertion since 1934 There were no attacks suggesting coronary occlusion The patient's

chief complaints were of dyspnea on exertion, dizziness and general weakness. There was no history of paroxysmal nocturnal dyspnea or congestive failure.

Physical examination revealed a well preserved asthenic man. Aicus senilis and kyphosis of the dorsal portion of the spine were noted. There was no congestion of the veins of the neck. The chest was clear. The heart was moderately enlarged. The apex beat was in the fifth intercostal space 12 cm from the mid-sternal line. There was no precordial thrill. An aortic second sound was faint over the aortic area. A loud rough systolic murmur was heard over the aortic area. There was a normal sinus rhythm. The blood pressure was 190 systolic and 100 diastolic. The radial and carotid arteries were thickened and tortuous. There was no pretibial edema.

An electrocardiogram showed a normal sinus rhythm. There was left axis deviation. The QRS interval was 0.14 second and the PR interval 0.18 second. The



Fig. 2—Roentgenographic appearance in case 2

QRS complex was notched and slurred in all leads. T_1 was inverted and opposite to the QRS deflection. There was left bundle branch block.

Roentgen examination of the heart revealed an aortic and tricuspid configuration, marked enlargement, moderate widening of the aorta, with dancing aortic calcifications, and pulmonary fibrosis (fig. 3).

CASE 4—J. C., aged 60, a seaman, first noticed symptoms of heart disease in 1925. On admission to the hospital he complained of dyspnea, palpitation and dizziness. There was no history of edema of the ankles or precordial pain. In 1934 he contracted a heavy cold, with a hacking cough, and since then had had increased dyspnea and had found it necessary to sleep on two pillows. During the past two years he had had three syncopal spells.

Physical examination revealed an emphysematous chest. The heart was slightly enlarged. The apex beat was noted in the fifth intercostal space 11 cm from the mid-sternal line. A systolic thrill was noted over the aortic area. The blood pressure was 120 systolic and 80 diastolic. There was a normal sinus rhythm, with occasional premature beats. An aortic second sound was not heard over the aortic area or over the vessels of the neck. There was a rough loud systolic

apical murmur, with a soft diastolic murmur over the aortic area. There was marked sclerosis of the radial and carotid arteries.

An electrocardiogram revealed a normal sinus rhythm and left bundle branch block. The PR interval was 0.18 second and the QRS complex 0.15 second. There

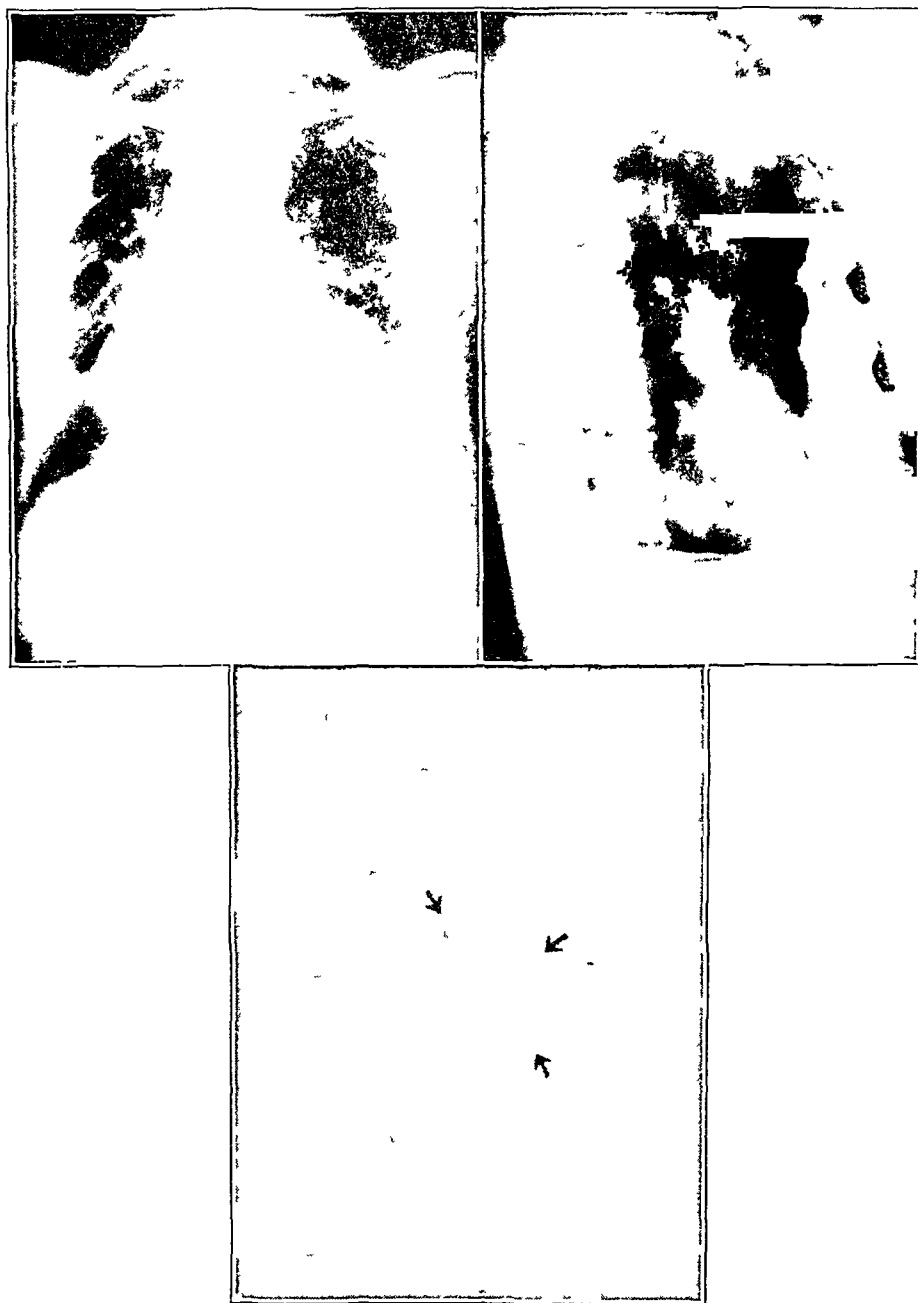


Fig. 3—Roentgenographic appearance in case 3

was left axis deviation. The QRS complex in all leads was notched and slurred. The ST segment was concave in lead I. T_1 and T_2 were upright. The T wave was opposite to the main deflection in leads I and III.

Roentgen examination demonstrated a hypertensive heart, with moderate enlargement. The aorta was moderately elongated and widened and of increased density and pulsation, with dense pulsating calcifications in the area of the aortic cusps. Pleural calcifications were present (fig 4). There was marked calcification of the tibial arteries.

CASE 14—J P, a man aged 68, was first seen in 1931. He had a history of epistaxis and shortness of breath for the past three months, which cleared up slowly with rest in bed and digitalis. There was no history of cardiac pain. The patient was readmitted to the hospital on Feb 2, 1935, with mild congestive failure and pretibial edema. Since then he has had exertional dyspnea. There was no history of rheumatic fever.

Physical examination revealed a well developed asthenic man. The pupils reacted equally to light and in accommodation. Examination of the fundus showed marked retinal sclerosis. There was no congestion of the veins of the neck. The

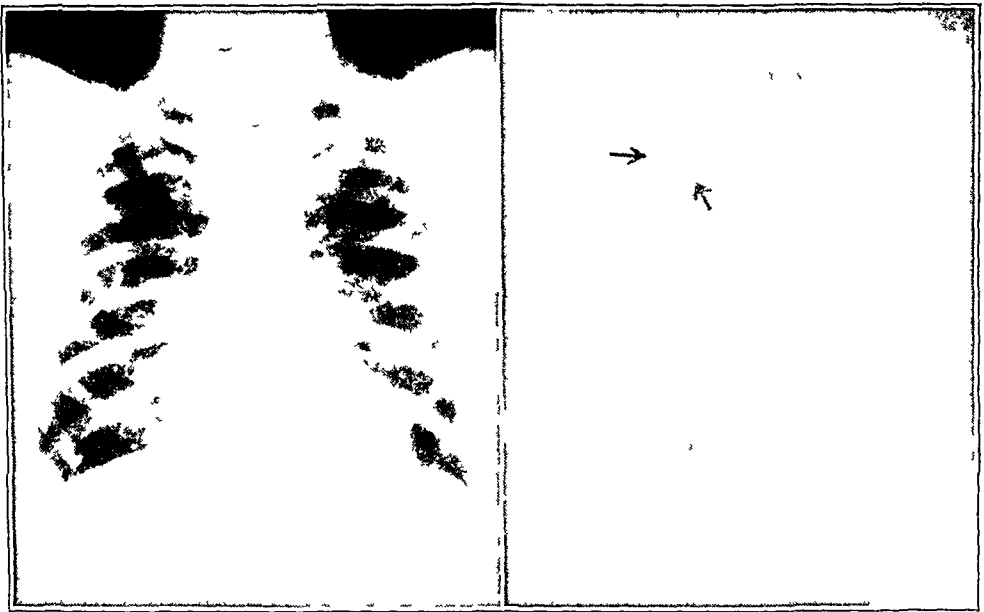


Fig 4—Roentgenographic appearance in case 4

lungs were resonant throughout. Examination of the heart showed that the point of maximal impulse was in the sixth intercostal space 12 cm from the midsternal line. There was a systolic thrill over the aortic area. An aortic second sound was faint but present over the vessels of the neck. There was a harsh loud systolic murmur over the mitral area. The sinus rhythm was normal. The blood pressure was 170 systolic and 90 diastolic. There was a small Corrigan pulse. Marked sclerosis of the radial arteries was noted.

The Wassermann reaction was negative. Uinalysis showed faint traces of albumin, with occasional hyaline casts.

Electrocardiograms were taken in 1931 and on March 13, 1937, and revealed a normal sinus rhythm, left axis deviation and no evidence of myocardial damage.

Roentgen examination revealed a normal pulmonary parenchyma (fig 6), moderate hypertrophy of the heart, accentuation of the left ventricular curve and slight dilatation and tortuosity of the aorta. Roentgenoscopy revealed a single sharply outlined density the size of a pea in the area of the aortic cusps, showing slow vertical oscillations independent of the respiratory excursions.

EXPLANATION OF FIGURE 5

Fig 5—*A*, case 1 Tracing made on April 10, 1935 Note the inversion of T in all leads *B*, case 1, Dec 10, 1936 *C*, case 1, March 5, 1937 Note that T is flat and markedly inverted in leads II and III *D*, case 4, April 2, 1934 Note the intraventricular block *E*, case 4, April 30 *F*, case 4, March 7, 1937 Note the left bundle branch block *G*, case 3, Oct 23, 1934 *H*, case 3, Feb 5, 1937 Note the left bundle branch block *I*, case 5, Feb 13, 1935 Note the inverted T₁, the diphasic T₂ and T₃ and the convex RT segment *J*, case 5, May 20 Note the inverted T₁ and T₂, the split QRS₃ and the diphasic T₃ *K*, case 6, March 27, 1933 Note the inverted T₁ and T₂ *L*, case 7, Oct 23, 1936 Note the intraventricular block, the diphasic T₁ and T₂, the notched and slurred QRS and the deflections in all leads

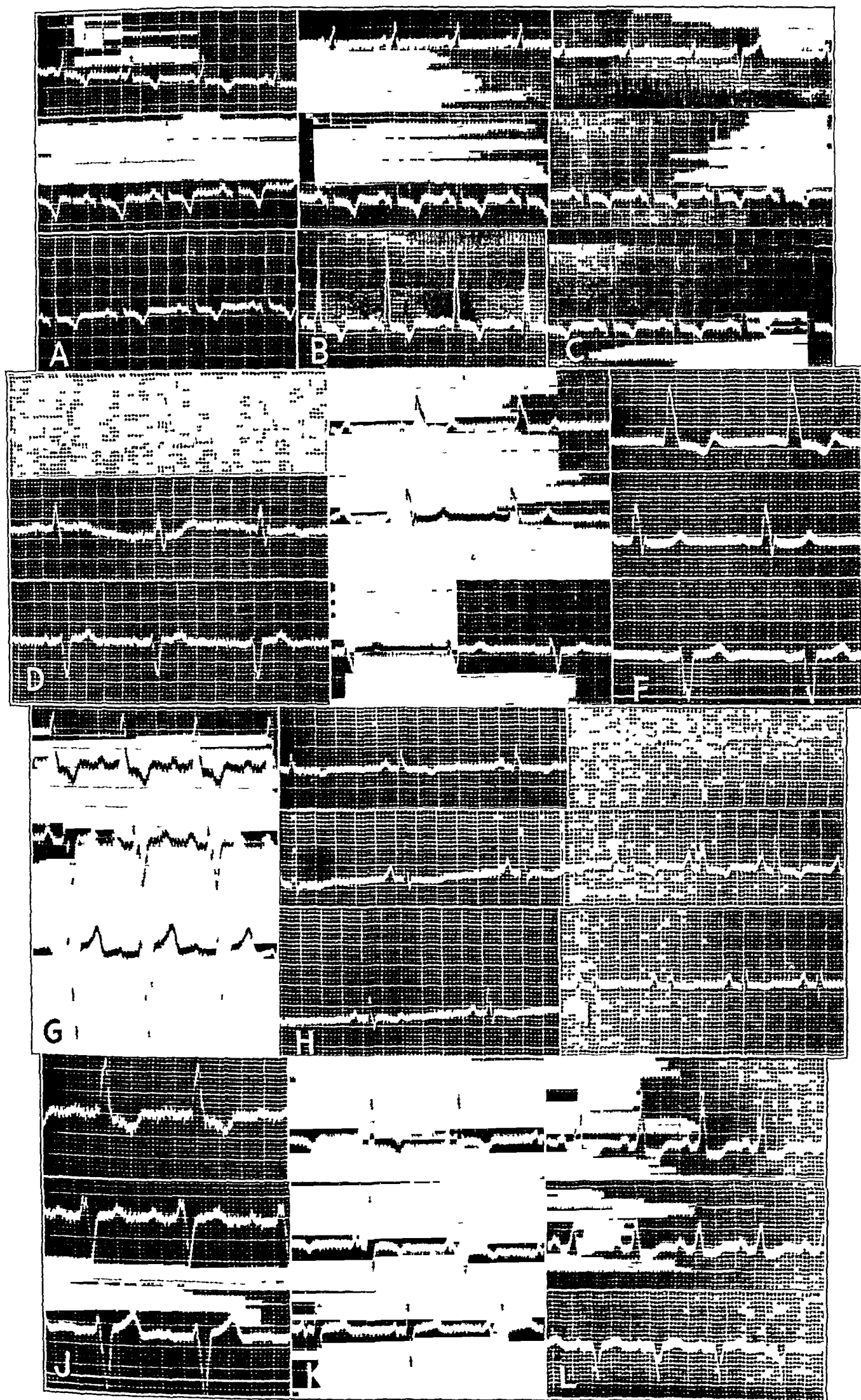


Figure 5

ELECTROCARDIOGRAPHIC CHANGES

The great majority of the changes in the electrocardiogram produced by calcific aortic valvulitis do not differ in any specific manner from some of those produced by myocardial disease due to coronary closure or by hypertrophy of the left ventricle. Electrocardiographic changes of the type most frequently seen with calcific aortic valvulitis consist of a modification of both the initial and the final deflection of the ventricular complex. The alterations which were noted are presented in detail.

T Wave—In case 1 there was an inverted T_1 , cove plane in T_2 and T_3 , characteristic of myocardial damage associated with disease of the coronary arteries. In this case the initial deflection (R summit) became

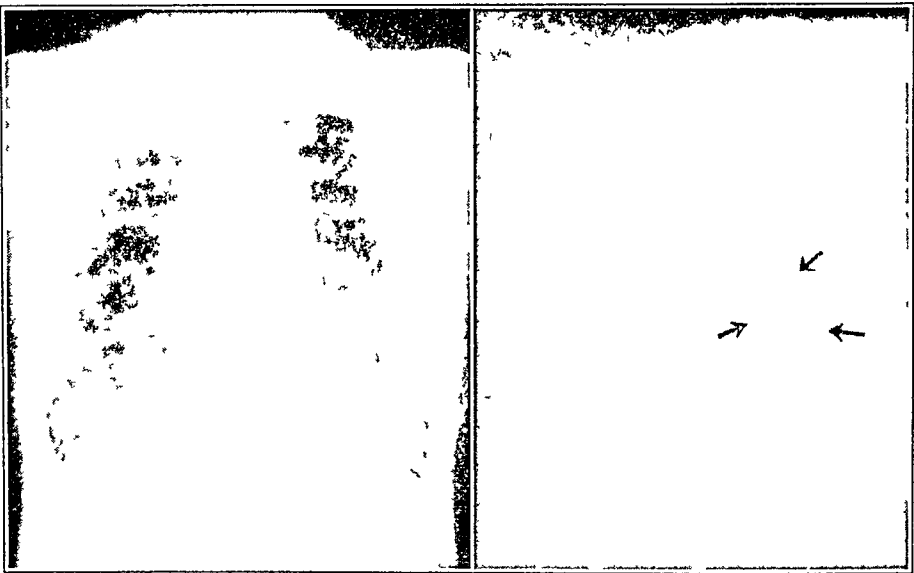


Fig 6—Roentgenographic appearance in case 14

smaller. In case 4, T_2 was diphasic and T_3 inverted, later changing so as to be typical of left bundle branch block, with T_1 inverted and T_3 upright (fig 5). There were the same electrocardiographic findings as noted in case 3. T_1 and T_2 were inverted in cases 5 and 6. Marked inversion of T_1 and T_2 and a diphasic T_3 were seen in cases 7 and 8. An upright T wave was seen in cases 2 and 14.

QT Interval—The QT interval has been used as a measure of electrical ventricular systole. This interval was found prolonged in cases of left bundle branch block, as seen in cases 3, 4 and 7.

PR Interval—The P wave was normal in all cases except case 3, in which there was a prolongation of the PR interval to 0.2 second.

QRS Complex—The QRS complex was normal in all but three cases (3, 4 and 7), in which characteristic findings of left bundle

branch block and intraventricular block were found. A depressed ST segment was found in case 7.

Arrhythmia—A normal sinus rhythm was present in all cases except for the occurrence of a ventricular extrasystole in cases 1 and 3.

Comment—The popular view, supported by many investigations, is that the electrocardiographic changes due to myocardial damage after coronary thrombosis are of two types: (a) inverted T_1 and T_2 (Q_1 , T_1 type) and (b) inverted T_2 and T_3 (Q_3 , T_3 type). There is still another type of old coronary thrombosis in which the electrocardiographic changes are not typical of these two types, and they may well be confused with the electrocardiographic changes of calcific aortic stenosis. There is sufficient similarity so that the two types might be confused if the electrocardiographic findings alone were considered. The fact that electrocardiographic changes persist over a long period without any change in the electrocardiogram is suggestive of their association with calcific aortic stenosis.

Left bundle branch block was seen in cases 3, 4 and 7 and was rather frequent (21 per cent) in our small group. With the possible exception of hypertensive heart disease, no other clinical entity produces left bundle branch block in such a high percentage of cases. The most likely explanation of left bundle branch block produced by calcific aortic valvulitis is that it is due to the involvement of the conduction system by large calcific projections of the aortic valve.

Although electrocardiographic changes produced by calcific aortic valvulitis are not characteristic of the classic type of acute coronary thrombosis, the findings are those usually considered to be characteristic of severe myocardial damage, with the inversion and coving of the T wave frequently seen with conditions causing hypertrophy of the left ventricle and with coronary thrombosis.

COMMENT

With the growing understanding of the clinical picture of calcific aortic valvulitis, it is increasingly evident that not infrequently the only clinical signs and manifestations are those of aortic regurgitation, and therefore an erroneous diagnosis is often made.

Although the most common etiologic factor in uncomplicated aortic valvulitis is syphilitic infection which produces a specific type of arteriosclerosis of the aorta and analogous scarring and retraction of the aortic valves, with separation of the commissures, this specific lesion practically never produces deposition of calcium in the valves such as is seen in calcific aortic stenosis.

In other words, pure aortic insufficiency, not due to syphilitic disease or to acute or subacute bacterial invasion of the valve, may be

due to calcific aortic valvulitis. This is especially true of the group of conditions which were formerly thought to be due to arteriosclerosis in which the signs of aortic stenosis were indefinite.

Frequently, aortic regurgitation is observed in middle aged or elderly adults, with or without hypertension, who show a negative Wassermann reaction, and is incorrectly diagnosed as sclerotic aortic regurgitation. A careful review of necropsy reports at Bellevue Hospital in cases of this type failed to confirm the clinical findings of arteriosclerotic aortic regurgitation. In all these cases necropsy revealed calcific aortic stenosis.

This new point of view throws further light on the early stage of the disease. Several of our patients have been followed for four or five years, with few clinical symptoms. Only in later life are there positive signs of aortic stenosis. Cardiac pain, heart failure and syncope occur late in the life cycle in this disease.

The electrocardiographic changes in many of our cases of calcific aortic stenosis are the same as those seen with myocardial damage associated with hypertrophy of the left ventricle and disease of the coronary arteries. This may be explained on the basis of interference with the coronary blood flow due to the large calcific projections of the aortic valve into the sinus of Valsalva, because the orifices and the lumens of the coronary arteries are well preserved and patent, as seen at necropsy in the majority of our cases. Another explanation is that the myocardium is suffering from anoxemia due to the hydrodynamic changes resulting from jet formation.

Marvin, in a review of his cases, attempted to explain the sudden death and syncope seen with aortic stenosis as due to hyperactivity of the carotid sinus reflex. We have not found in our cases any abnormality of this reflex. It would also be possible to explain syncope and cardiac death as due to morphologic changes involving the cardiac muscle and its conduction system.

The association of syncope and cardiac pain in these subjects is frequently mistaken for coronary thrombosis. The correct diagnosis of calcific aortic valvulitis is frequently made only at necropsy, especially if the physical signs of aortic stenosis are indefinite.

If it is borne in mind that electrocardiographic tracings with these two conditions may be similar, the use of roentgenoscopy and aimed roentgenography may help to detect the calcific depositions and lead to a correct diagnosis.

SUMMARY

Fourteen cases of calcific aortic stenosis are reported, with clinical and electrocardiographic findings and nine autopsy examinations. Roentgen diagnosis was made in the remaining five cases.

Today careful clinical and roentgenographic examination make it possible to diagnose calcific aortic stenosis in vivo as a routine procedure. In our series a clinical diagnosis of arteriosclerotic aortic regurgitation or myocardial infarction was invariably made.

In a certain group of cases of calcific aortic stenosis the only clinical manifestations are those of aortic regurgitation.

In some of our cases electrocardiographic changes were presented which did not differ in any specific manner from those due to myocardial changes associated with disease of the coronary arteries. The presence of cardiac pain and syncope in these cases may lead to the erroneous diagnosis of coronary thrombosis.

We wish to emphasize, therefore, that in cases of aortic regurgitation in which there are electrocardiographic findings of myocardial damage and no evidence of syphilitic or rheumatic heart disease, a proper roentgenoscopic and roentgenographic examination may reveal characteristic depositions in the aortic valves.

OSSEOUS FORM OF GAUCHER'S DISEASE

REPORT OF A CASE

S MELAMED, M D

NEW YORK

AND

WILLIAM CHESTER, M D

MAMARONECK, N Y

An excellent review of the osseous form of Gaucher's disease may be found in the article by Ludwig Pick¹ We are reporting this case of Gaucher's disease because of the extensive osseous changes and the unusual hematologic findings

REPORT OF CASE

Sidney F, a Polish Jew, 26 years of age, was admitted for the last time to the Montefiore Hospital on Nov 28, 1934 His parents and four brothers and sisters were living and well

History—In 1921 he was incapacitated by intermittent pain, swelling and at times redness, commencing in the knee joints and soon involving the hips, shoulders, elbows and ankles There was no fever The arthritic pains were believed to be rheumatic In 1922 a diagnostic puncture of the enlarged spleen showed the patient to be suffering from Gaucher's disease During the next four years the articular pains recurred frequently and with increasing severity Progressive enlargement of the spleen and marked pallor were noted In 1926 severe nasal and oral hemorrhages occurred There was marked enlargement of the abdomen and at times urinary incontinence In 1928, because of the hemorrhagic phenomena, consequent anemia and symptoms of pressure from the greatly enlarged spleen, this organ was removed After splenectomy the hemorrhages ceased, the anemia disappeared and the patient experienced relief from the articular pains and gained weight From 1928 to 1930 he was frequently hospitalized because of recurring pains in the joints In 1930 he was again hospitalized because of pain in the back At this time a gibbus was noted in the dorsal region In 1931 hepatic enlargement appeared In 1932 walking was difficult even with the aid of a back brace In 1933 a fracture of the sternum, with regional swelling of the soft parts, was noted By 1934 the patient's height had decreased from 60 to 40 inches (150 to 100 cm) For eight months he had been bedridden A blood-tinged expectoration, associated with a rise in temperature to 102 F, interpreted as due to bronchopneumonia, had troubled him for three months At the time of his last admission to the hospital, weakness and skeletal pains were his chief symptoms

Examination—Physical examination revealed a poorly nourished man The skin was yellowish brown, dry and inelastic Bilaterally a pinguecula was present

From the medical service of Dr Leopold Lichtwitz, Montefiore Hospital

1 Pick, L Ergebn d inn Med u Kinderh 29 519, 1926

at the inner canthus. There was marked pallor of the conjunctival and oral mucous membranes. Numerous small discrete nontender shotty glands, ranging from the size of a pea to that of a hazelnut, were felt in the cervical, axillary and inguinal regions.

The thoracic cage was considerably deformed. Marked dorsal kyphosis extended from the sixth to the tenth dorsal vertebra. Lordosis was present in the lumbar region. The anteroposterior diameter of the chest was increased. There was flaring of the lower ribs. Tenderness to pressure was present from the sixth to the tenth dorsal vertebra. There were dullness, rales, increased tactile fremitus and increased breath and voice sounds at the base of the right lung.

Examination of the heart revealed no abnormality. The blood pressure was 104 systolic and 76 diastolic. A scar from a left rectus incision was present. The liver was smooth and slightly tender and extended into the right iliac fossa. The left lobe was felt beneath the left costal margin. There was slight clubbing of the fingers. Neurologic examination revealed no abnormality.

Laboratory Data—On December 14 a blood count showed hemoglobin, 48 per cent (7.2 Gm), red blood cells, 2,900,000, nucleated cells (red and white), 23,000, white blood cells, 6,000, nucleated red blood cells, 17,000, platelets, 90,000, segmented polymorphonuclears, 20 per cent, staff cells, 20 per cent (only 50 white cells were counted), lymphocytes, 40 per cent, monocytes, 20 per cent, and reticulocytes, 6 per cent (half with and half without nuclei). The red blood cells showed marked anisocytosis and poikilocytosis. Their size was slightly below normal. Polychromasia and basophilic stippling were present. Occasional Howell-Jolly bodies were seen (fig. 1). The platelets were larger than normal and did not stain as dark as usual.

The bilirubin content of the blood was 0.3 mg per hundred cubic centimeters, and the icterus index, 4.

Blood fragility and resistance tests showed beginning hemolysis with 0.44 per cent solution of sodium chloride (with 0.44 per cent solution for a control subject) and complete hemolysis with 0.28 per cent solution of sodium chloride (with 0.32 per cent solution for a control subject). The results of the Hamburger test are shown in figure 2. There was a marked shift to the right, indicating an increased resistance of the red blood cells. The bleeding time was two minutes, the coagulation time, one minute, and the clot retraction time, one hour. The tourniquet test gave negative results.

From the foregoing data it was concluded that there was marked hypochromic microcytic anemia, characterized by dysfunction of the bone marrow rather than an increase in the destruction of blood. There was a remarkable outpouring of immature red blood cells, as evidenced by the polychromasia, the basophilic stippling, the reticulocytes, the normoblasts and the increased resistance of the red blood cells. Slight lymphocytosis and thrombopenia were noted but no corresponding purpuric changes.

Chemical analysis of the blood showed sugar, 80 mg, urea nitrogen, 11.3 mg, calcium, 10.4 mg, phosphorus, 2.9 mg, cholesterol, 138 mg, and cholesterol esters, 101 mg, per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

According to the congo red method, the cell volume was 28 per cent and the plasma volume 72 per cent. The plasma volume was estimated at 35 cc per kilogram of body weight and the total blood volume at 50 cc per kilogram. The congo red test showed that 90 per cent of the dye remained in the blood stream after one hour. There was no amyloidosis.

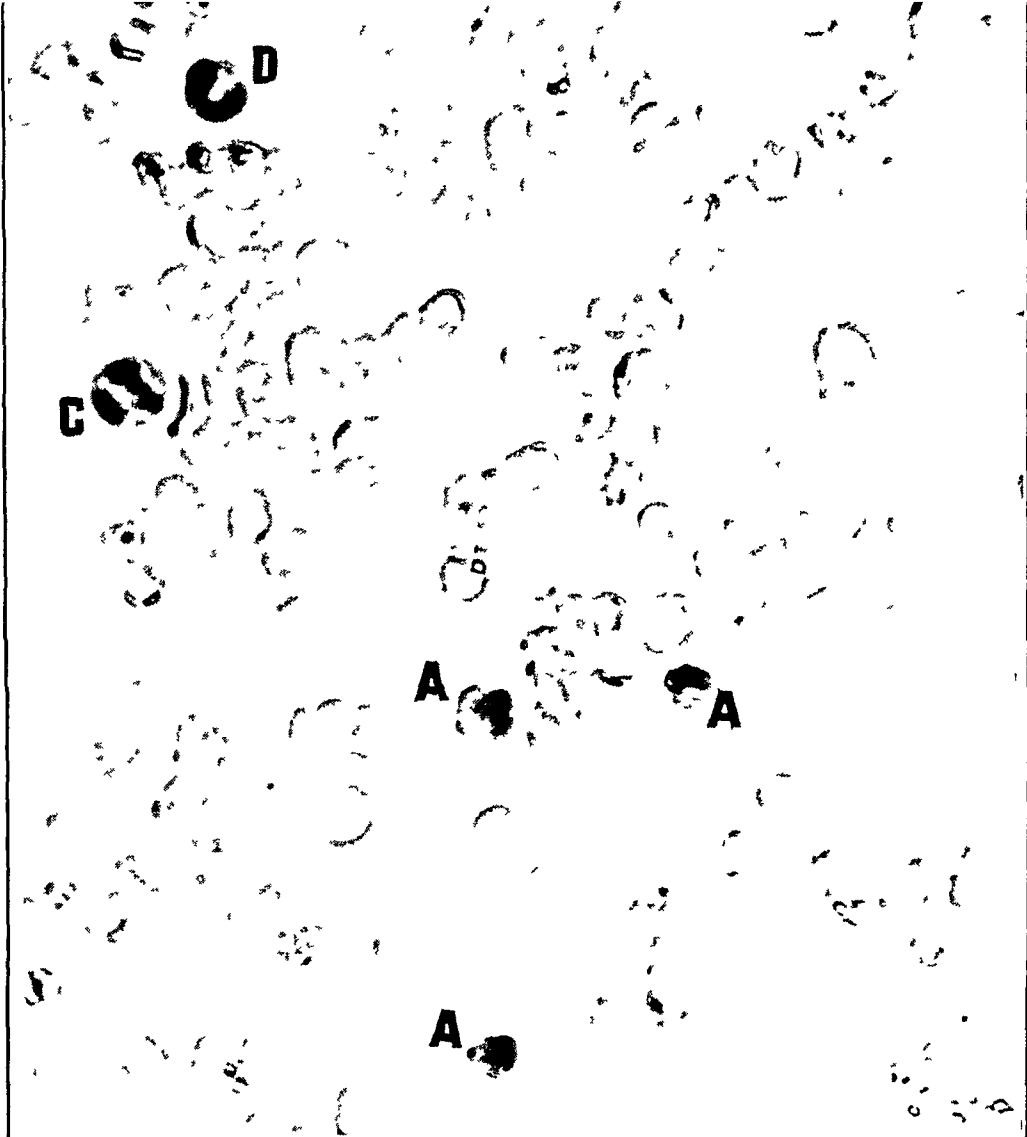


Fig 1—Blood smear *A* indicates nucleated red blood cells, *B*, a red blood cell, *C*, a polymorphonuclear cell, *D*, a polymorphonuclear staff cell

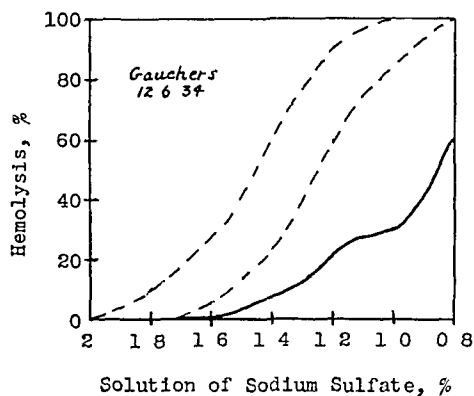


Fig 2—Chart showing the fragility of the red blood cells in solutions of sodium sulfate. The values along the ordinate indicate the percentage of hemolysis. The values along the abscissa indicate the percentage of the solution of sodium sulfate. The broken lines indicate the limits of the normal values. The solid line indicates the patient's curve, showing the increased resistance.

Hepatic function tests showed no bile in the urine, a marked increase of the urobilin content and a marked increase of the urobilinogen content (1:300 dilution [normal, 1:10 or 1:20]) The bromsulphalein excretion test showed that 50 per cent of the dye remained in the blood stream after a half hour This was abnormal All these findings indicated hepatic dysfunction

Urinalysis showed specific gravity, 1.013 to 1.028, albumin, + to ++, and sugar, 0 Microscopic examination revealed no abnormality

The electrocardiogram showed left axis deviation

The basal metabolic rate was +44 and +40 per cent, respectively, on two occasions, and the oxygen consumption was 317 and 325 liters, respectively

Röntgen examination of the skeleton showed extensive changes There was marked destruction of the fifth dorsal vertebra The body of the seventh dorsal vertebra was collapsed to one third its normal size, it was somewhat elongated and extended slightly beyond the borders of the contiguous vertebral bodies The body of the ninth dorsal vertebra showed marked absorption The bodies of the eleventh dorsal and of the first lumbar vertebra were collapsed to about one-third their normal size The space between the twelfth dorsal and the first lumbar vertebra was obliterated Absorption and some narrowing of the body of the fourth lumbar vertebra was present (fig 3)

The pelvis showed cystic changes in both innominate bones, especially in the region of the acetabulum and of the pubic bones Small areas of osteosclerosis were also present Hypertrophic arthritic changes were noted in the left sacro-iliac synchondrosis (fig 4)

The femurs showed marked involvement The head of the left femur was irregular in outline and flattened and showed areas of bone sclerosis as well as cystic areas The shaft was broadened and showed marked cystic areas The distal end was bottle shaped and showed areas of absorption The right femur was similarly involved

The left tibia showed areas of osseous absorption in the proximal and middle thirds Slight bowing of the shaft of the left fibula was present Areas of osseous absorption were noted in the middle third of the right tibia

The right humerus showed areas of absorption in the head and neck and bone sclerosis in the upper third of the shaft

Absorption of bone was noted in the lower end of the left radius

All the ribs showed marked calcium absorption

A pathologic fracture of the first dorsal vertebra was noted on Jan 15, 1935

The skull was normal

Course—During his stay in the hospital the patient complained of skeletal pains and marked weakness A productive cough and pitting edema of the ankles were present On April 16 the temperature rose to 104 F and remained slightly elevated the next day On April 18 he was confused, and he had spells of vomiting and expectorated blood-tinged sputum Stiffness of the neck, stupor and a temperature of 96 F were present on April 20, the day of death

The hematologic data obtained during the patient's stay in the hospital are charted in the accompanying table As can be seen, the anemia became progressively worse, the number of normoblasts fell considerably, the red blood cells changed from microcytes to macrocytes and abnormal white blood cells appeared

Postmortem Examination—The autopsy was performed by Dr Henry Unger Only the essential data are presented here

The diagnosis was as follows Gaucher's disease (osseous type), with involvement of the liver, lymph nodes, spinal column, pelvis, left femur, right humerus

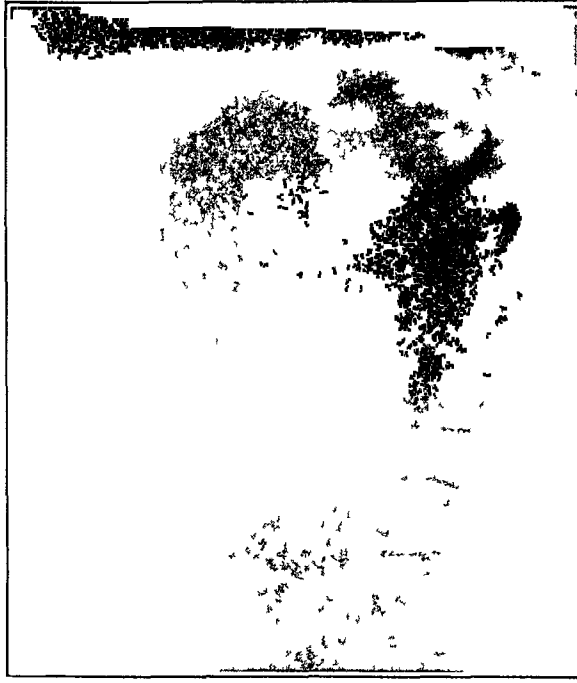


Fig 3—Roentgenogram of the spine

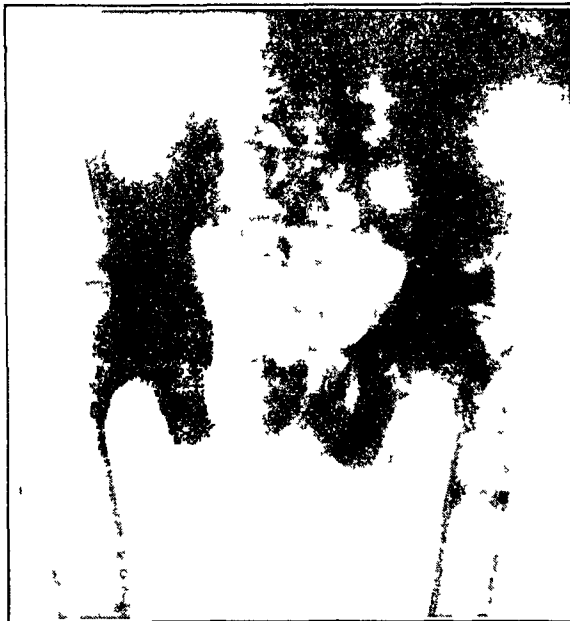


Fig 4—Roentgenogram of the pelvis

and left radius, status postsplenectomy, heterotopic bone-marrow formation in the liver, bronchopneumonia, and bronchiolitis obliterans

The liver weighed 4,100 Gm and extended into the right iliac fossa. The capsule was smooth and translucent. The cut surface showed the parenchyma to be almost completely replaced by irregular confluent waxy-colored areas interspaced with yellow areas. In some places the lobular structure was still evident. The periportal regions were widened and pale yellow. A reddish area, the size of a walnut and well demarcated from the parenchyma, was present in the right lobe. Microscopically the periportal spaces showed an increase in connective tissue, in which numerous Gaucher cells were embedded. In places the nests of Gaucher

Summary of Data

Date	Hospital*	Hemoglobin, %	Erythrocytes, Million	Leukocytes, Thousand	Polymorpho-nuclears, %			Eosinophils	Myelocytes, %	Myeloblasts, %	Lymphocytes, %	Monocytes, %	Reticulocytes, %	Platelets, Thousand	Normoblasts per 100 Leukocytes	Bleeding Time, Minutes	Clotting Time, Minutes	Tourniquet Test
					Segmented	Stab	Young											
8/24/25	M S	50	3.2	6	41						57	2		140	0	2.5	3.5	+
1/23/23	J	55	3.4	4	36						60	4	5	300	0	2.0	9.0	
								Splenectomy										
2/ 9/28	J	52	3.8	11	74		4	1	4.0		17			350	0	1.0	2.0	
4/ 4/28	J	75		11	65						35							
1/30/30	J	66†	4.2	10	50			3			40	7	1	180	2	1.0	4.0	
2/21/31	J	74†	4.0	11†											10			
12/26/31	M S	79	5.1	14	47						49	3	2		8	1.5	7.0	—
1/10/32	M S	80						Normal										
1/29/32	M S	83	5.1	18	72	12					12	4						
5/13/32	J	70	4.6												3			
4/30/33	M S	85	4.5	10	39	5					52	4	3	260	32			
7/17/33	M S	74		13	58													
12/18/33	M S	75		11	67						30	3			213			
12/20/33	M S	80	4.7	13	47			5			45	3	9		200			
4/17/34	J	61†	4.2	16†	52				2.5		38			250	20	0.7	5.0	
9/10/34	J	45‡													75			
9/15/34	J	58	2.8															
10/ 2/34	J	55	4.0											90				
12/14/34	M	45‡	2.9	6†	20	20					40	20	6	90	280			
2/ 2/35	M			18	10		5	2	8.0	2	50	5			190			
3/ 4/35	M	37‡	2.4	12†	60		1		2.0	2	26				210			
4/ 2/35	M	25‡	2.1‡	9†	52	10	3		1.0	4	25	5			71			

* M S indicates Mount Sinai Hospital J, Jewish Hospital M Montefiore Hospital

† Dares hemoglobinometer

‡ Corrected white blood cell count

§ Sahli hemoglobinometer

|| The erythrocytes showed definite macrocytosis

cells compressed the hepatic cells. The circumscribed area in the right lobe proved to be heterotopic bone marrow and contained cells of the myelopoietic and erythropoietic series.

The lymph nodes (mediastinal, tracheobronchial, iliac, inguinal and mesenteric) were soft and somewhat enlarged. The cut surfaces were bright yellow. Microscopic examination showed that only a few of the follicles were preserved. The sinuses were widened and contained numerous large mononucleated and multinucleated Gaucher cells and some lymphocytes. The reticulum was filled with large clusters of Gaucher cells. The reaction for iron pigment was strongly positive.

The osseous system showed marked involvement. A sharp gibbus was noted in the upper dorsal region and a forward bulge of the sternum in the region of the manubrium sterni.

There was marked destruction of the vertebrae from the fifth dorsal to the first lumbar vertebra (fig 5). The cut surface of the upper thoracic vertebrae was pinkish and contained small yellowish foci, the lower thoracic and lumbar vertebrae were filled with very friable granular yellowish red tissue. The cancellous tissue was readily removed, leaving only a thin cortical shell. Some of the intervertebral disks were completely separated from their contiguous vertebrae. For the most part, the disks were preserved, however, some of them were flattened and showed an absence or herniation of the nucleus pulposus. On the posterior aspect, between the third and the fourth lumbar vertebra, the disk was flat, and

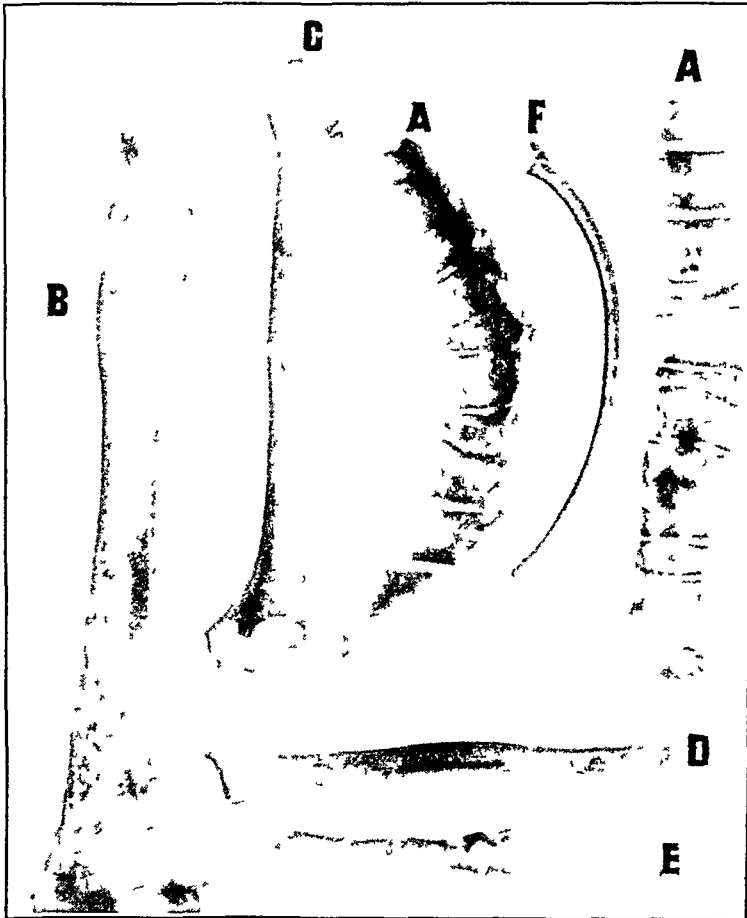


Fig 5—Roentgenographic appearance of the anatomic specimens A, vertebral column, B, left femur, C, right humerus, D, right radius, E, sternum, F, rib

the nucleus pulposus had expanded and herniated into the third lumbar vertebra. The disks between the twelfth dorsal and the first lumbar vertebra and between the first and the second lumbar vertebra were partially resorbed, the remaining portions herniating into the contiguous vertebrae, which were eburnated.

The fourth, sixth and seventh dorsal and the second and third lumbar vertebrae were examined histologically. The cortex of the fourth dorsal vertebra was, for the most part, intact. The medullary cavity showed marked resorption of the horizontal trabeculae, considerable fibrosis and round cell accumulations. The fibrous ring of the intervertebral disk was invaded by numerous blood vessels

The sixth and seventh dorsal vertebrae, in addition to the changes previously enumerated, showed numerous Gaucher cells in the medullary cavity. The second and third lumbar vertebrae showed marked rarefaction of the trabeculae of the cortex and medulla. Large necrotic areas were present in the cortex and in the medulla. The intervertebral disk was highly vascularized. The nucleus pulposus showed partial fibrosis and was invaded by numerous mononuclear elements.

The cortex of the manubrium sterni was thinned out, and a fracture was present in the midregion (fig 5). The cancellous bone was broken down, and the pinkish marrow was soft. The cortex of the body of the sternum showed irregular thickening.

The costochondral junction of the fifth rib was sharply demarcated. The medulla was narrow. Near the cartilage there was some softening.

The head of the right humerus contained a soft red area the size of a cherry. The rest of the head was sclerotic, and there was a marked increase of the bony trabeculae. The lumen of the proximal diaphysis was narrowed, and in places the cortex and medulla were fused. The medullary cavity of the shaft contained yellow and red-mottled friable material. The humeroscapular and elbow joints appeared normal (fig 5).

The medullary cavity of the left radius was narrowed, and the density of the cancellous bone was increased. At the level of the tuberosity there was an area of bright yellow friable tissue the size of an almond surrounded by a thin red zone.

The head of the left femur was markedly flattened. The lower proximal portion of the articular surface was completely destroyed, and the cartilage was absent. Beneath the area of the most marked depression of the head of the femur was an area of softening, the size of a navy bean, filled with soft, elastic translucent grayish pink tissue. In the medial region of the head several nodules of friable yellowish tissue completely replaced the normal structure. The upper third of the shaft was widened, and the medullary cavity in the proximal half was filled with well delineated brownish red and yellow tissue. In the distal half, small dark red cystic areas surrounded by bright yellow zones were present (fig 5).

The heart showed fatty infiltrations of the wall of the right ventricle.

The lungs showed patches of bronchopneumonia and areas of bronchiolitis obliterans.

COMMENT

Because of the long-standing presence of normoblasts noted when the patient was in the other institutions, we assumed the following to be the course of events. The patient had the typical pathologic changes seen in Gaucher's disease. Splenectomy was performed in February 1928 because of the hemorrhagic manifestations. One and a half months after splenectomy the anemia disappeared. No early records of the hematologic findings were available. On Jan 30, 1930, two years after splenectomy, an almost normal hemoglobin value was noted, together with the presence for the first time of normoblasts (fig 6). From then on, for almost five and a half years, normoblasts were constantly present in the peripheral blood stream. At first their number was small, but they suddenly appeared in great numbers on Dec 20, 1933 (200 per hundred white blood cells). As soon as this occurred, anemia reappeared and became progressively worse. Six months before death the number

of normoblasts began to diminish. An interesting feature was the appearance of macrocytosis at the end of the patient's life, in April 1935.

The platelets remained normal until the last six months of life, when thrombopenia appeared. Of interest is the fact that the patient had purpura before splenectomy was performed, with a normal platelet count, and that when thrombopenia developed there were no purpuric manifestations, again showing that the number of platelets is not the only factor concerned in purpura.

The white blood cell count did not show any marked changes. At first there was the typical tendency toward leukopenia and lymphocytosis.

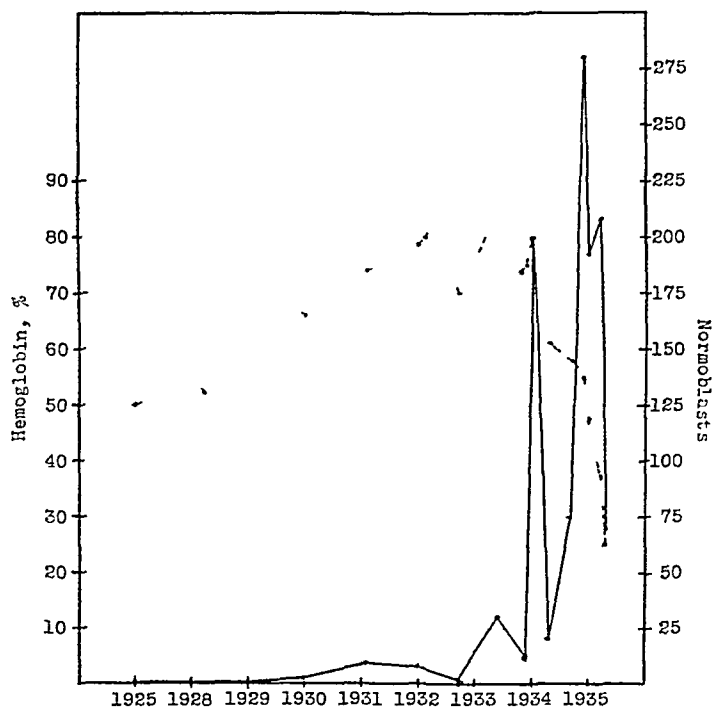


Fig 6—Chart showing the relation of hemoglobin to normoblasts. The values along the left ordinate indicate the hemoglobin values, and the values along the right ordinate, the number of normoblasts per hundred white blood cells. The broken line indicates the curve for hemoglobin and the solid line the curve for normoblasts.

Leukocytosis was present postoperatively and during the course of various infectious episodes. The leukocytosis persisted but was due to the large number of nucleated red blood cells. The true white cell count remained low (there was almost leukopenia). Toward the end of life (1935) myelocytes and myeloblasts appeared.

Study of the course of events, then, shows that after splenectomy the anemia disappeared. But this "cure" of the anemia was only apparent. The infiltrations by specific Gaucher tissue in bone marrow, liver and lymphatic glands continued. Because of the resulting mechani-

cal pressure, the bone marrow was functioning under difficulties. The red blood cells persisted and functioned longer because of the removal of the hemolytic activity of the spleen. The essential lesion in the bone marrow progressed. The red blood cells became increasingly immature, the hemoglobin balance being maintained despite these difficulties. In order to maintain this balance, the number of nucleated red blood cells constantly increased. However a limit was reached, and finally anemia reappeared, despite the normoblasts. Later, even the production of platelets and of white blood cells was affected.

Another interesting finding was hepatic dysfunction, as shown by the abnormal detoxifying function test (bromsulphalein), the urobilinogen in the urine and the macrocytosis of the red blood cells. Anatomically, infiltration of the liver with Gaucher tissue, cirrhosis of the liver and a heterotopic nodule of bone marrow were noted. It seems that the body economy had reverted to embryonal blood formation in the liver to overcome the inability of the bone marrow to maintain hemoglobin equilibrium.

The extensive skeletal involvement is worth emphasizing. The collapsed vertebra and subsequent changes in the contiguous intervertebral disks may present a roentgen picture similar to that in cases of Pott's disease. The osteoplastic changes in the proximal portion of the right humerus are a rarity in Gaucher's disease. The arthritic involvement in early childhood, interpreted as rheumatic fever, reemphasizes the importance of the role of diseases of metabolism in the causation of the arthropathies.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1937

ASHTON GRAYBIEL, M D

WITH THE EDITORIAL ASSISTANCE OF

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BOSTON

PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Recent improvements in technic have made possible certain studies¹ on the dynamics of the pulmonary circulation in dogs under more nearly normal conditions than heretofore. It has been found that the velocity of the pulse wave in the pulmonary arteries is about the same as that in the aorta at the physiologic pressures existing in each. However, at comparable pressures the velocity is much greater in the pulmonary arteries than in the aorta, which suggests that in low pressure ranges the large pulmonary arteries are less easily distended than is the aorta. Variations in the pressure in the pulmonary arteries with respiration are in the same direction as the variations in the pressure in the systemic arteries, falling in inspiration and rising in expiration. The variations in the pulmonary arteries are probably the direct result of changes in intrathoracic pressure rather than the indirect result of respiratory fluctuations in systemic venous flow. Suddenly increasing the systemic arterial pressure by the administration of epinephrine causes only a slight rise in the pressure in the pulmonary arteries. Thus the right ventricle is spared the sudden strain to which the left ventricle is subjected. This sparing action is due in part to the lowering of systemic venous pressure, in part to the ability of the left ventricle to adjust the force of its ejection to the arterial resistance, but, above all, to the great capacity of the pulmonary bed, enabling it to increase its blood content considerably without a great rise in pressure. Under asphyxial conditions the systemic arterial pressure first rises and then falls. The pressure in the pulmonary arteries and veins does not rise significantly till the systemic arterial pressure starts falling. Thus, under various adverse conditions the weaker, right ventricle is protected by the buffer effect of the pulmonary circuit.

From the Cardiac Clinic of the Massachusetts General Hospital

1 Johnson, V, Hamilton, W F, Katz, L N, and Weinstein, W. Studies on the Dynamics of the Pulmonary Circulation, *Am J Physiol* **120** 624, 1937

McMichael,² and Sweeney and Mayerson³ have made careful studies of the postural changes in cardiac output in man. The results of previous investigations have not been uniform, although the majority have indicated that the output decreases after the subject changes from the lying to the sitting or the erect position. This conclusion has been upheld by the aforementioned authors, and their studies have indicated that the amount of the fall is usually from 2 to 30 per cent. Sometimes this fall may be masked by the increased rate of consumption of oxygen usually found when the subject is in the standing position.

Gibson and Evans⁴ have used a modification of the dye method in the determination of the plasma and of the total blood volume which has given reliable results. It was found that in normal adults the total volume of blood varies within wide limits. In males the average is 777 and in females 661 cc per kilogram of body weight, the difference being due largely to the greater volume of red blood cells in males. It was further found that no relation exists between variations in total blood volume, venous pressure and velocity of blood flow but that the relation of blood volume to height or surface area offers a useful basis for the estimation of the normal blood volume.

Evans and his associates have shown that the working heart utilizes not only dextrose but lactate. Under resting conditions the lactate content of the blood is at its basic level, and its usage by the heart is small. During strenuous muscular exertion, however, the lactate content of the blood is enormously increased, and the heart then uses considerable amounts of that substance and, moreover, uses it in preference to dextrose and in larger amounts. Now it is known that the glycogen content of the heart working under relatively normal conditions is well maintained, and it is a matter of importance to know the relation between the glycogen content of the heart and the sugar and lactate content of the blood.

This problem has been carefully studied by Bogue, Evans and Gregory.⁵ They availed themselves of the fact that the continuous

2 McMichael, J. Postural Changes in Cardiac Output and Respiration in Man, *Quart J Exper Physiol* **27** 55, 1937.

3 Sweeney, H. M., and Mayerson, H. S. Effect of Posture on Cardiac Output, *Am J Physiol* **120** 329, 1937.

4 Gibson, J. G., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J Clin Investigation* **16** 301, 1937, II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, *ibid* **16** 317, 1937.

5 Bogue, J. Y., Evans, C. L., and Gregory, R. A. The Source of Heart Glycogen, *Quart J Exper Physiol* **27** 27, 1937.

administration of epinephrine rapidly depletes cardiac glycogen⁶ By using dog heart-lung preparations it was found that heart failure rapidly sets in when the glycogen reaches a low level, suggesting that cardiac muscle is incapable of functioning in the absence of glycogen Addition of lactate after epinephrine depletion of cardiac glycogen leads to no recovery of glycogen, although there is evidence that the lactate is utilized in muscular contraction Addition of dextrose after glycogen depletion results in considerable restoration of glycogen, showing that this substance is formed from dextrose Addition of both dextrose and lactate to a glycogen-depleted heart leads to a smaller formation of glycogen than is obtained with dextrose alone, because higher concentrations of lactate depress the utilization of sugar

The polemic regarding the incidence and significance of blood vessels in human cardiac valves, which began nearly a century ago, still exists Gross⁷ concluded from his extensive studies that blood vessels do not exist in normal valves or that if they do they must be rare He further concluded that a heart which has so-called normal vascularized valves presents widespread stigmas of healed rheumatic fever He has cited his reasons for believing that rheumatic fever which has gone on to complete healing is responsible for the formation of these blood vessels

On the other hand, Wearn and his co-workers⁸ have reemphasized that blood vessels are frequently present in normal cardiac valves The occurrence and distribution of vessels in the valves were studied in 255 hearts revealing no evidence of inflammatory disease and in 78 hearts recognized as being or as having been the seat of inflammation Sixty-six per cent of the hearts which showed no evidence of inflammatory disease revealed vascularization of one or more valves, about half of which were vascularized beyond the proximal third of the leaflets or cusps Of especial interest in proving that this vascularization is not the result of unrecognized inflammation was the discovery that in 12 of 49 infants under 1 year of age one or more of the cardiac valves were vascularized beyond the proximal third Of the hearts which showed evidence of inflammatory disease, 88 per cent revealed vascularization of one or more valves, and 69 per cent revealed one or more valves that were vascularized beyond their proximal third The frequency with which the various valves are vascularized follows the same sequence in the two groups, the mitral valve having the highest incidence, followed by the tricuspid, pulmonic and aortic valves

6 Chang, I The Influence of Adrenaline on Cardiac Glycogen, *Quart J Exper Physiol* **26** 285, 1937

7 Gross, L Significance of Blood Vessels in Human Heart Valves, *Am Heart J* **13** 275, 1937

8 Wearn, J T, and Moritz, A R The Incidence and Significance of Blood Vessels in Normal and Abnormal Heart Valves, *Am Heart J* **13** 7, 1937

In deciding between these two authoritative reports it is our opinion that the positive findings of Wearn have the advantage over the negative findings of Gross

Shipley and his associates⁹ have found that during the normal growth of the rabbit heart the muscle fibers enlarge and the capillaries multiply, so that a relatively constant capillary supply per unit of tissue is maintained from the time of birth to maturity. In cardiac hypertrophy the muscle fibers enlarge beyond the normal, but the capillaries do not multiply, with the result that the capillary supply per unit of tissue is reduced. It is pointed out that in the hypertrophied heart the relatively decreased capillary supply constitutes an impediment to the exchange of metabolic substances.

MacMahon¹⁰ was prompted to study the problem of normal and pathologic growth of cardiac muscle elements by the observation of an unusually large number of mitoses in the myocardial fibers of the enlarged heart of a 6 month old child. Careful histologic examination of 2 other enlarged hearts, of infants of 12 and 20 months of age, respectively, revealed the presence of mitoses in all stages of nuclear division. Isolated mitotic figures were also observed in the heart of a boy 6 years of age who died several days after the onset of diphtheria. The mitoses were present in muscle fibers which bordered zones of destruction. MacMahon's observations are of unusual interest as many investigators have painstakingly searched throughout the myocardium of patients with cardiac hypertrophy without finding any positive evidence, in the form of mitoses, of proliferation of muscle fibers.

Comeau¹¹ has described 2 cases of diffuse parietal endocardial sclerosis and has reviewed the cases described previously.

Golden and Brams¹² were able to find in the medical literature of the last century only 38 reports of cases in which the heart weighed 1,000 Gm or more. Details of 9 additional cases are given. Of especial interest is the fact that the enlargement in only 1 of these 9 was associated with pericardial adhesions, while about half of those previously reported were supposedly due to pericardial adhesions alone or in combination with valvular disease. Aortic regurgitation of syphilitic origin and aortic stenosis of rheumatic origin are the common causes of massive cardiac enlargement aside from adhesive pericarditis.

9 Shipley, R. A., Shipley, L. J., and Wearn, J. T. The Capillary Supply in Normal and Hypertrophied Hearts of Rabbits, *J. Exper. Med.* **65**:29, 1937.

10 MacMahon, H. E. Hyperplasia and Regeneration of the Myocardium in Infants and in Children, *Am. J. Path.* **13**:845, 1937.

11 Comeau, W. J. Diffuse Parietal Endocardial Sclerosis. Review of the Literature and Report of Two Cases, *Am. J. Path.* **13**:277, 1937.

12 Golden, J. S., and Brams, W. A. Extreme Cardiac Enlargement, *Am. Heart J.* **13**:207, 1937.

METHODS, SYMPTOMS AND SIGNS

Kerr and his associates¹³ have devised a modified stethoscope, termed the symballophone, which can be used to determine the point of origin of sounds and the direction of propagation. Preliminary observations have indicated that this device will be useful in studying heart sounds and murmurs.

Sprague¹⁴ has reviewed the subject of the mechanism of production of cardiac murmurs. Of especial interest is the discussion of certain factors modifying the audibility of murmurs. For example, the extreme softness or absence of a diastolic murmur of aortic regurgitation in many instances of aortic stenosis is probably due to the damping effect of the cone-shaped valves directed against the current, augmented by the damping effect of the funnel-shaped opening into the left ventricle from the aorta. Again, in instances of mitral stenosis associated with high blood pressure in the left auricle, the mitral regurgitant murmur may be greatly damped because the entrance of a jet of fluid into a chamber where the pressure is high causes less murmur. The question of functional murmurs has been ably discussed by the author.

Lian¹⁵ has described 3 cases in which continuous murmurs were best heard in the second or third intercostal space to the right of the sternum. He has given his reasons for believing that these murmurs originated in the superior vena cava, probably as a result of compression of this vessel, and that they were analogous to the continuous murmurs sometimes heard over the jugular vein in the neck. Lian¹⁶ has further described 2 cases in which continuous murmurs were heard over the right interscapulovertebral space and has explained their presence as being due probably to compression of a pulmonary vein. We are reminded of a case in which a loud continuous murmur was heard over the lower right portion of the thorax posteriorly, necropsy did not reveal anything which would serve as an explanation.

Dressler¹⁷ has described, with considerable accuracy, the pulsations of the wall of the chest as they are found normally and in certain

13 Kerr, W. J., Althausen, T. L., Bassett, A. M., and Goldman, M. J. The Symballophone. A Modified Stethoscope for Lateralization and Comparison of Sounds, *Am Heart J* **14** 549, 1937.

14 Sprague, H. B. The Mechanism of the Production of Heart Murmurs, in Kerr, W. J. *Modern Concepts of Cardiovascular Disease*, New York, American Heart Association, 1937, vol. 6.

15 Lian, C. Le souffle continu cave supérieur, *Bull et mem Soc med d hôp de Paris* **53** 1088, 1937.

16 Lian, C. Le souffle veineux continu de l'espace interscapulo-vertébral droit, *Bull et mem Soc med d hôp de Paris* **53** 1100, 1937.

17 Dressler, W. Pulsations of the Wall of the Chest. I. General Consideration, *Arch Int Med* **60** 225 (Aug.) 1937, II. Pulsations Associated with Aortic

types of heart disease Although it is good to have on record a correct analysis of these pulsations, the practical value of such knowledge is small

ROENTGENOLOGY

Roesler¹⁸ has written the most authoritative book in the English language on the subject of cardiovascular roentgenology This book has been adequately reviewed in many medical journals

One of the most important studies that have been reported during the past year was Palmer's¹⁹ on the development and progression of cardiac enlargement in heart disease as determined from serial teleroentgenograms The material has been well arranged and concisely dealt with and is of great practical value Of especial interest were the findings in cases of hydrothorax due to heart failure, in which, contrary to expectation, appreciable cardiac displacement was not found to occur About the only statement with which we are not in agreement is that in coronary disease, enlargement of the heart may be due to chronic myocardial ischemia alone Of the 5 cases illustrating this conception, complications were present in every one, coronary thrombosis in 4 and chronic congestive failure in 1 other

The more significant conclusions are worth quoting

In the majority of cases of congestive failure no decrease was noted in the size of the heart after clinical improvement When regression did occur, it was usually general, involving both borders, but chiefly the right auricle and superior vena cava

Although the evidence is yet inconclusive, some degree of permanent enlargement probably often remains as a result of, and after recovery from, prolonged bouts of congestive failure, such as are found in mitral stenosis and in hyperthyroidism with auricular fibrillation Short bouts of failure, e g, in prolonged attacks of paroxysmal tachycardia, are without permanent effect on the size of the heart

No example could be found of a right-sided hydrothorax in failure causing displacement of the right border of the heart, or of the heart as a whole, to the left On the contrary, the right border was often moved to the right, apparently influenced by elevation of the diaphragm

Regurgitation, *ibid* 60 437 (Sept) 1937, III Pulsations Associated with Tricuspid Regurgitation, *ibid* 60 441 (Sept) 1937, IV Pulsations Associated with Adhesive Pericardial Disease, *ibid* 60 654 (Oct) 1937, V Pulsations Associated with Mitral Regurgitation and Aneurysmal Dilatation of the Left Auricle, *ibid* 60 663 (Oct) 1937

18 Roesler, H Clinical Roentgenology of the Cardiovascular System, Springfield, Ill, Charles C Thomas, Publisher, 1937

19 Palmer, J H The Development of Cardiac Enlargement in Disease of the Heart A Radiological Study, Medical Research Council, Special Report Series, no 222, London, His Majesty's Stationery Office, 1937

Enlargement of the heart in paroxysmal tachycardia is referable to the super-vention of congestive failure in a prolonged attack, for otherwise it is minimal or absent

Established auricular fibrillation and flutter usually, but not always, cause enlargement. When enlargement develops it is almost invariably associated with signs of congestion in one or both of the pulmonary and systemic circuits. Radiologically the enlargement is found to involve most frequently the right auricle, superior vena cava, pulmonary arc, and less often the left auricle. The enlargement in these arrhythmias is probably bound up with and indicative of coincident failure.

Wherever the heart assumes a so-called characteristic radiological shape, notably in valvular lesions, the local changes in chamber size involved in the determination of this shape are the first changes to take place. Further enlargement of the X-ray shadow tends to be more or less equally distributed on all cardiac borders (general enlargement), thus preserving, though in a modified form, the shape peculiar to the disease. After the apex has reached the left axilla, progressive enlargement continues to the right.

General enlargement was the type most often encountered during the investigation. It was due, both in the later stages of slowly developing enlargement, and in the more rapid enlargement associated with such conditions as the onset of auricular fibrillation, chiefly to the participation of more than one chamber in the process.

Another factor tending to bring about an appearance of general enlargement is the ability of the fibrous pericardium so to distribute intra-pericardial tension by causing alteration in position of the heart in the pericardial sac that localised increase in cardiac size may result in displacement of all borders of the radiological shadow in some measure.

The impression was gained that there is in young persons a greater tendency than in older ones towards development of enlargement under similar conditions. In this connection the single case of rapid and great hypertrophy in a child with hypertension is significant.

In essential hypertension cardiac enlargement appears to develop simultaneously and equally with the gradual rise of blood-pressure to a permanent fixed level during months or years. Progressive enlargement in uncomplicated cases does not easily occur after the blood-pressure level has become stabilized.

Most examples of progressive cardiac enlargement were seen in diseases known to be progressive in the pathological sense, chiefly rheumatic valvular lesions and coronary sclerosis. This observation, taken in conjunction with the findings that enlargement often failed to progress in stabilized hypertension, in syphilitic aortic incompetence where there was apparent clinical arrest of the lesion, and in gross aneurysm of the myocardial wall following coronary thrombosis, lends support to the view that enlargement evoked in response to a certain burden does not progress if the burden is not increased. It may be assumed that whenever progressive enlargement is discovered either the original lesion is progressive in character or some new factor has become operative.

So-called acute dilatation of the heart, that is, gross enlargement developing in a few hours or days, is rare. It never seems to arise at the onset or during the course of abnormal rhythms where it might be expected, nor in the later stages of chronic cardiac disease. The nearest approach to it seems to be the rapid enlargement shown by Dorner to develop within a few days in severe diphtheria.

ELECTROCARDIOGRAPHY

Joint recommendations²⁰ for the use of a single precordial lead (called lead IV) as a routine have been made by committees acting for the American Heart Association and the Cardiac Society of Great Britain and Ireland. In addition to these joint recommendations the American committee²¹ has had published a more extended account with reference to multiple precordial leads and to the theoretic considerations on which these recommendations are based.

For ordinary use the following recommendations apply. The apical electrode should be circular and between 2 and 3 cm in diameter. It should be placed over the extreme outer apical border of the heart as determined by palpation. If the palpation is unsatisfactory the apical border of the heart should be determined by some other means. The paired electrode preferably should be placed on the left leg, in which case the lead is designated as IV F. If other locations for the indifferent electrode are selected, they should carry the designation B for interscapular region, R for right arm and L for left arm. Galvanometric connections should be made in such a way that the relative positivity of the apical electrode is represented in the electrocardiogram by an upward deflection. The deflections in the precordial lead should be designated P, Q, R, S and T, respectively, just as in the case of the limb leads. Normally the QRS wave of this new lead IV is diphasic, with an upright first phase, R, and the T wave is upright. The report of the American committee should be consulted for details concerning the employment of multiple chest leads.

Gilson and Bishop²² have presented a convincing argument that the dipole theory of tissue potentials, which attempts to explain the genesis of the electrocardiogram, is inadequate. They have stated the opinion that the classic hypothesis, or the hypothesis of so-called negativity, should not be abandoned on the basis of arguments offered in support of the dipole theory.

Katz²³ has presented a summary of his views in regard to the genesis of the electrocardiogram. It is especially emphasized that the electrocardiogram is a record of events in favored rather than in all regions

20 Standardization of Precordial Leads. Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *Am Heart J* **15** 107, 1938. Standardization of Precordial Leads, *J A M A* **110** 395 (Jan 29) 1938.

21 Standardization of Precordial Leads. Supplemental Report, *J A M A* **110** 681 (Feb 26) 1938.

22 Gilson, A. S., and Bishop, G. H. The Effect of Remote Leads upon the Form of the Recorded Electrocardiogram, *Am J Physiol* **118** 743, 1937.

23 Katz, L. N. Concerning a New Concept of the Genesis of the Electrocardiogram, *Am Heart J* **13** 17, 1937.

of the heart. Currents due to injury and affecting these favored regions are revealed, but those in other areas may be missed.

Abramson and Jochim²⁴ have stated that they are not in agreement with current concepts regarding the impulse spread in the ventricles. Their experimental data have justified the belief that the impulse does not leave the subendocardial Purkinje network to spread out and over the muscle itself but remains in this network and excites the muscle in numerous places almost simultaneously, also, that the impulse spread has no relation to the direction of the muscle bundles. These experimental data confirm the anatomic observations of Abramson and Margolin²⁵.

We feel that despite wide differences in opinion regarding the intimate nature of the electrocardiogram its clinical value remains about the same because clinical electrocardiography is largely empiric. These differences also form a strong argument for the importance of continuing to collect such empiric clinical data.

Robb and Robb²⁶ have reemphasized that when the R peaks of the electrocardiogram are out of phase, there exists no satisfactory method for calculating the electrical axis. Thus unless E_2 equals E_1 plus E_3 , the R peaks are out of phase, and each R may have an axis of its own that differs about 50 to 100 degrees from those of the others. It is suggested that in these instances the method used in calculating the axis should be indicated.

Lambert²⁷ stated that he was persuaded on the basis of animal experimentation and clinical observation that certain alterations in the P wave and in the PR segment may occur as a result of ischemia of the auricular musculature. These alterations are, notably, a notching or inversion of the P wave and depressions of the PR segment which are analogous to changes in the ST segment. The significance of such alterations is lost, however, unless normal sinus rhythm is present. Also certain normal variations of the P wave must be kept in mind such as slight notching in any lead and inversion in lead III.

Barker, Johnson and Wilson,²⁸ and Hegglin and Holzmann²⁹ have reemphasized the fact that the Q to T interval of the electrocardiogram

24 Abramson, D. I., and Jochim, K. The Spread of the Impulse in the Mammalian Ventricle, *Am J Physiol* **120** 635, 1937.

25 Abramson, D. I., and Margolin, S. A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricles, *J Anat* **70** 250, 1936.

26 Robb, R. C., and Robb, J. S. The Electrical Axis in Simultaneous Leads. I. Factors Increasing the Dispersion of Normal Values, *Am Heart J* **14** 588, 1937.

27 Lambert, J. Les alterations d'origine coronarienne du complexe electrocardiographique auriculaire. Etude experimentale et clinique, *Arch d mal du cœur* **30** 3, 1937.

28 Barker, P. S., Johnson, F. D., and Wilson, F. N. The Duration of Systole in Hypocalcemia, *Am Heart J* **13** 82, 1937.

is abnormally prolonged in the presence of abnormally low levels of calcium in the blood serum. This, as an incidental finding, may lead to the recognition of otherwise unsuspected conditions associated with hypocalcemia.

Mussen³⁰ found that in rabbits, after orthostatic collapse or after the administration of histamine in large doses, there regularly appeared in the electrocardiogram lowering of the ST segment in leads I and II which was sometimes associated with inversion of the T waves. Histologic examination of the cardiac muscle of animals which survived the histamine or orthostatic collapse revealed disseminated anoxic necrosis.

Akesson³¹ has reported the finding of an inverted T wave in lead II or III of the electrocardiograms of apparently normal persons which changed to normal when there was a shift from the upright to the recumbent position. He concluded that this apparent abnormality, which suggests coronary disease, may be dependent on relative myocardial ischemia due to what he has called orthostatic arterial insufficiency.

CARDIAC ARRHYTHMIAS

Dumitresco-Mante³² has studied the problem of icteric bradycardia. From clinical and experimental observations he concluded that icteric bradycardia is neurogenic, resulting from disequilibrium between the vagus and the sympathetic nerves but with the vagal tonus predominating. This disequilibrium is believed to be due to the increase in the content of choline and potassium in the blood rather than any change in concentration of the bile salts or calcium.

Harvey³³ has pointed out that in many instances of paroxysmal tachycardia the auricular complex is not clearly discernible in the three conventional electrocardiographic leads and for this reason the cardiac rhythm cannot be determined with certainty. Cases are presented illustrating the manner in which this difficulty was overcome with the aid of esophageal leads.

29 Hegglin, R., and Holzmann, M. Die klinische Bedeutung der verlängerter QT-Distanz (Systolendauer) im Elektrokardiogramm, *Ztschr f klin Med* **132** 1, 1937.

30 Mussen, H. Ueber Coronarinsuffizienz nach Histamin-Collaps und nach orthostatischen Collaps, *Beitr z path Anat u z allg Path* **99** 329, 1937.

31 Akesson, S. Ueber Veränderungen des Elektrokardiogramms bei orthostatischer Zirkulationsstörung, *Upsala lakaref forh* **41** 383, 1936.

32 Dumitresco-Mante, M. La bradycardie et le syndrome humoral au cours des ictères du type catarrhal, *J de physiol et de path gen* **35** 14 and 416, 1937.

33 Harvey, A. McG. The Origin of Paroxysmal Tachycardias as Determined by the Esophageal Electrocardiogram, *Ann Int Med* **11** 57, 1937.

We suggest that in many cases, at least, this technic is unnecessary because a well defined auricular wave may be obtained in a precordial lead by placing one electrode in the third or fourth interspace just to the right of the sternum

Campbell³⁴ and Lyon³⁵ have reported observations on patients with paroxysmal tachycardia with a very rapid heart rate. The nature of these arrhythmias is often difficult to determine even from electrocardiograms. Usually the paroxysms consist of either auricular tachycardia or auricular flutter and are more likely to be associated with a diseased than with a healthy heart. Cardiac symptoms usually appear unless the attack is short lived.

Brill³⁶ has reviewed in a concise manner the knowledge concerning auricular fibrillation from a clinical aspect.

Sprague³⁷ has described an unusual instance of auricular fibrillation and bundle branch block. After the administration of digitalis the auricular fibrillation ceased, but the bundle branch block persisted and was associated with a short PR interval. This strange association has been shown to occur in apparently healthy persons, and the importance of its proper recognition is apparent.

Comeau³⁸ has critically reviewed the medical literature on recurrent complete heart block alternating with normal conduction and accompanied by the Adams-Stokes syndrome. Two additional cases are reported, and certain practical and therapeutic considerations are emphasized.

Hoff and Nahum³⁹ have analyzed the cardiac irregularities produced in rabbits after the administration of calcium salts. In the non-anesthetized animal, after the injection of 20 cc of a 10 per cent solution of calcium chloride, auricular fibrillation developed in each instance, as well as frequent premature beats and various grades of auriculoventricular block. Previous atropinization prevented auriculoventricular block and auricular fibrillation but promoted the development of ventricular extrasystoles and occasionally precipitated ventricular

34 Campbell, M. Paroxysmal Tachycardia in Infants, *Guy's Hosp Rep* **87** 205, 1937.

35 Lyon, J. A. Excessively Rapid Heart Rates. Report of a Case with Autopsy, *J A M A* **108** 1393 (April 24) 1937.

36 Brill, I. C. Auricular Fibrillation. The Present Status, with a Review of the Literature, *Ann Int Med* **10** 1487, 1937.

37 Sprague, H. B. Auricular Fibrillation and Bundle Branch Block in an Apparently Normal Heart. A Case Report, *Internat Clin* **1** 187, 1937.

38 Comeau, W. J. Paroxysmal Heart Block Alternating with Normal Rhythm and Conduction, *Am J M Sc* **194** 43, 1937.

39 Hoff, H. E., and Nahum, L. H. An Analysis of the Cardiac Irregularities Produced by Calcium and Their Prevention by Sodium Amytal, *J Pharmacol & Exper Therap* **60** 425, 1937.

tachycardia and ventricular fibrillation Sodium amytal in narcotic doses was found to suppress all cardiac irregularities due to calcium chloride and to prevent arrest of the heart, which is probably to be attributed to the depression of both vagal and sympathetic activity

CONGENITAL HEART DISEASE

Yater and Shapiro⁴⁰ have reported a typical example of Ebstein's disease and have summarized the data regarding 15 previously reported cases This disease is a rare congenital anomaly, consisting essentially of downward displacement of the tricuspid valve in an otherwise completely developed heart Commonly associated findings are patent foramen ovale and enlargement of the right auricle

Clinical diagnosis of this disease seems impossible, although it may be suspected The enlargement of the heart is not characteristic Usually there is a loud systolic murmur heard best at the level of the third or fourth intercostal space near the sternum, occasionally both systolic and diastolic murmurs are heard with or without an accompanying thrill The pulmonic second sound is usually not accentuated Cyanosis and clubbing of the fingers may or may not be present Signs of tricuspid insufficiency usually appear only when congestive heart failure is precipitated This condition is compatible with long life, and pulmonary tuberculosis appears as a frequent complication

RHEUMATIC HEART DISEASE

Etiologic Factors—There has been further evidence against the concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection Finkle,⁴¹ and Faulkner and Taylor,⁴² who have studied the relation of vitamin C and infection, have found no evidence that vitamin C deficiency has a causal relation to any pathologic condition other than scurvy and that the effect of rheumatic fever on vitamin C metabolism appears to be the same as that of other infectious diseases McBroom and his associates⁴³ have studied acute scurvy produced in guinea pigs with and without superimposed infection It was concluded that although scurvy may indirectly be a factor

40 Yater, W M, and Shapiro, M J Congenital Displacement of the Tricuspid Valve (Ebstein's Disease) Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System, *Ann Int Med* **11** 1043, 1937

41 Finkle, P Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, *J Clin Investigation* **16** 587, 1937

42 Faulkner, J M, and Taylor, F H L Vitamin C and Infection, *Ann Int Med* **10** 1867, 1937

43 McBroom, J, Sunderland, D A, Mote, J R, and Jones, T D Effect of Acute Scurvy on the Guinea-Pig Heart, *Arch Path* **23**:20 (Jan) 1937

in lowering the general resistance of the body to infection, there is as yet no evidence of a direct causal relation between this disease and rheumatic fever

Eagles and his co-workers⁴⁴ have presented evidence which, they concluded, supports the possibility that rheumatic fever is due to a virus infection. Suspensions of particles bearing a close resemblance to elementary bodies of known virus infection were prepared from exudates obtained from patients with acute rheumatic fever, rheumatoid arthritis and chorea. These particles were found to be agglutinated by serum from patients suffering from the corresponding disease. Cross agglutination occurred within the whole group with sufficient regularity to point to an interrelation. Various control suspensions were in no case agglutinated by any of the known serums. Agglutination of suspensions of exudates from patients with rheumatic fever by serum from patients with rheumatic fever occurs in various types of the disease in the active stage and also when it has become inactive. The number of serums giving a positive agglutination reaction is about equal to the number of those showing no agglutination. When individual serums were tested at intervals throughout several weeks, it was not possible to correlate the presence or absence of agglutination with any definite phase of the clinical condition. We wish to add that other investigators, using essentially the same material and methods, have not been able to substantiate these results.

A number of interesting reports⁴⁵ have appeared showing the influence of climate and race on rheumatic heart disease. Of especial interest is Paul and Dixon's survey among American Indian school children in northern and southern localities. It was found that in the cold though relatively dry climate of the northwestern localities the incidence of rheumatic heart disease is high (4.5 per cent), whereas in the warm and dry climate of the southwestern localities the incidence is low (0.5 per cent). In localities between these extremes the incidence of rheumatic heart disease is 1.9 per cent. Furthermore, it is probable that the clinical course of the disease is milder in southwestern than in northern localities. Even allowing for possible sources of error, it is apparent that the incidence of rheumatic heart disease is many times greater in the North than in the South.

44 Eagles, G. H., Evans, P. R., Fisher, A. G. T., and Keith, J. D. A Virus in the Aetiology of Rheumatic Diseases, *Lancet* **2** 421, 1937.

45 Paul, J. R., and Dixon, G. L. Climate and Rheumatic Heart Disease. A Survey Among American Indian School Children in Northern and Southern Localities, *J. A. M. A.* **108** 2096 (June 19) 1937. Chang, F. C., and Dieuaide, F. R. Clinical Study of Rheumatic Fever, *Chinese M. J.* **51** 581, 1937. Maddox, K. Metropolitan and Rural Incidence and Distribution of Acute Rheumatism and Rheumatic Heart Disease in New South Wales, *M. J. Australia* **1** 394, 1937.

Pathologic Changes —Waalér,⁴⁶ in a study of the superior vena cava at its entrance into the right auricle, observed rheumatic lesions in 8 of 73 cases of rheumatic carditis. These lesions have some of the features of the lesions of auricular rheumatic endocarditis and also of rheumatic aortitis which have been described. In 8 additional cases hyaline plaques were observed, but it was undecided whether they represented the final and healed stage of the acute rheumatic lesions or whether they were sclerotic.

Gross and Silverman⁴⁷ have studied the inflammatory changes observed in the aortic commissures in 70 cases of rheumatic fever. The pathogenesis of these commissural lesions was discussed, and it appears that even though the original infection may reach the aortic ring through several routes, in most instances the inflammatory granulation tissue passes from the pericardial mantle through the aortic root, wedge and annulus to reach the aortic ring.

Rae⁴⁸ has described some unusual pathologic changes seen in a young child who died of acute rheumatic fever with pancreatitis. Marked acute inflammatory lesions of a proliferative, degenerative and necrotic character involved the main coronary arteries. Large aneurysmal dilations in the right coronary artery and in the descending branch of the left coronary artery were observed. Thrombosis occurred in the right coronary aneurysm without causing myocardial infarction. Although the possibility that these aneurysms were of congenital origin cannot be denied, it is much more likely that they resulted from rheumatic infection.

Massell and his associates⁴⁹ demonstrated that the subcutaneous injection of the patient's own blood, with subsequent frictional pressure, resulted in the appearance of a nodule in the immediate area in 37 of 82 subjects with rheumatic fever and chorea. A definite relation was found between the activity of the process of rheumatic fever and the induction of nodules. Thus, the appearance of nodules in 90 per cent of the patients with clinically active rheumatic fever and in 50 per cent of those with only laboratory evidence of active rheumatic fever was in striking contrast to their appearance in only 14 per cent of the subjects without evidence of active rheumatic fever and in 14 per cent of the

46 Waalér, A. Morphological Changes in the Superior Vena Cava and Right Auricle in Rheumatic Heart Disease, *Am J Path* **13** 855, 1937.

47 Gross, L., and Silverman, G. The Aortic Commissural Lesion in Rheumatic Fever, *Am J Path* **13** 389, 1937.

48 Rae, M. V. Coronary Aneurysms with Thrombosis in Rheumatic Carditis, *Arch Path* **24** 369 (Sept.) 1937.

49 Massell, B. F., Mote, J. R., and Jones, T. D. The Artificial Induction of Subcutaneous Nodules in Patients with Rheumatic Fever, *J Clin Investigation* **16** 125, 1937.

subjects with chorea. A nodule appeared in only 1 of the 34 control subjects. The duration of these induced nodules varied from a few weeks to several months, and the clinical course was comparable to that when nodules appeared spontaneously.

Mote and his associates⁵⁰ found that there is a great similarity of pathologic structure between induced and spontaneously occurring nodules of similar age.

Collins⁵¹ has reported his studies on the examination and comparison of nodules from patients with rheumatoid arthritis and rheumatic fever and nodules arising as the result of injury alone. Certain differences were noted, but he concluded that there was enough evidence to postulate either a close pathologic relation or a common etiologic factor of the nodules in rheumatoid arthritis and those in rheumatic fever.

Course and Prognosis—A number of reviews and statistical analyses⁵² have appeared bearing on the clinical course of rheumatic fever. Little that is new has been added. One point that probably should be emphasized even more strongly than heretofore is the great tendency to recurrences after the initial attack of acute rheumatism in children. They should be kept under close observation at least until past puberty, when the tendency toward recurrence is decreased.

Complications—Graef and his co-workers⁵³ have studied carefully the problem of auricular thrombosis in hearts showing evidence of rheumatic disease. This complication was present in 24 of the 178 hearts studied. Of the 24 instances of auricular thrombosis, congestive heart failure was associated in 21, auricular fibrillation in 18, mitral stenosis in 18, active rheumatic carditis in 14 and macroscopic auricular scarring in 22. Although all these factors appear to favor the development of auricular thrombi, the persistence of active inflammation appears to be the chief one.

50 Mote, J. R., Massell, B. F., and Jones, T. D. The Pathology of Spontaneous and Induced Subcutaneous Nodules in Rheumatic Fever, *J. Clin. Investigation* **16**: 129, 1937.

51 Collins, D. H. Subcutaneous Nodule of Rheumatoid Arthritis, *J. Path. & Bact.* **45**: 97, 1937.

52 Cushing, H. B. Rheumatic Fever and Heart Disease in Children, *Canad. M. A. J.* **37**: 311, 1937. Conner, L. A. Comments upon Certain Aspects of Rheumatic Fever and Rheumatic Heart Disease, *New England J. Med.* **217**: 503, 1937. Coburn, A. F., and Moore, L. V. The Independence of Chorea and Rheumatic Activity, *Am. J. M. Sc.* **193**: 1, 1937. Roth, I. R., Lingg, C., and Whittemore, A. Heart Disease in Children, *Am. Heart J.* **13**: 36, 1937. Leonard, M. Puberty and Prognosis in Rheumatic Fever, *ibid.* **14**: 192, 1937.

53 Graef, I., Berger, A. R., Bunim, J. J., and de la Chapelle, C. E. Auricular Thrombosis in Rheumatic Heart Disease, *Arch. Path.* **24**: 344 (Sept.) 1937.

Levine and White⁵⁴ have reported their findings regarding pulmonary infarction as a complication of severe disease of the mitral valve. Five fatal cases have been reported in detail, including the necropsy data. Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis showed that pulmonary infarction occurred in 61 per cent of the 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension there were 39 instances of congestive failure, in 21 of which there was pulmonary infarction. Pulmonary infarction is a common complication of congestive failure from any cause but particularly when mitral stenosis is present, it is often overlooked and may account for the inability of the failing heart to respond to treatment.

Harvier and his associates⁵⁵ have discussed the occurrence of functional pulmonary regurgitation as a complication of mitral stenosis. The difficulties in clinical diagnosis have been emphasized, especially the difficulty in differentiating the Graham Steell murmur from that of aortic regurgitation. A case has been described wherein roentgen kymography confirmed the clinical interpretation that pulmonary rather than aortic regurgitation was present. A plea has been made for the further employment of this diagnostic method in all such cases.

Contratto and Levine⁵⁶ made a study of 180 patients with aortic stenosis, unassociated with any other significant valvular disease, 53 of whom were examined post mortem. They concluded that the etiologic factor in most cases was previous rheumatic infection. In about half the cases an aortic diastolic murmur was not audible. Angina pectoris occurred in nearly a fourth of the cases, and the presence of normal coronary vessels in 2 of the young patients and only minimal atheroma in the vessels of some of the others that had angina pectoris strongly suggested that the deformity of the valve itself was in some way responsible. The frequent absence (19 of the 41 instances) of aortic insufficiency in this group of patients with angina pectoris was of especial interest.

Treatment—Sadow and her co-workers⁵⁷ have shown that a diet that has a high caloric value and that is optimal in all nutritional elements is beneficial in the treatment of rheumatic fever. This conclusion

54 Levine, H. B., and White, P. D. Pulmonary Infarction Complicating Severe Disease of the Mitral Valve, *Arch Int Med* **60** 39 (July) 1937.

55 Harvier, P., Mallarmé, J., and Ledoux-Lebard, G. Artérite pulmonaire avec insuffisance fonctionnelle de l'orifice pulmonaire dans le rétrécissement mitral à propos d'un cas avec radiokymographie, *Paris méd* **1** 397, 1937.

56 Contratto, A. W., and Levine, S. A. Aortic Stenosis, with Special Reference to Angina Pectoris and Syncope, *Ann Int Med* **10** 1636, 1937.

57 Sadow, S. E., Hubbard, J. P., and Jones, T. D. A Dietary Study in Rheumatic Fever, *New England J Med* **217**:170 1937.

was based on the fact that the gain in weight with such a diet was greater than with the usual hospital diet although no observable difference in the course of the disease was seen

Barnacle, Ewalt and Ebaugh,⁵⁸ and Kendell and Simpson⁵⁹ have reported favorably on the treatment of chorea with artificial fever. This has confirmed the favorable results previously reported.

Levy and Golden⁶⁰ have reported favorable results of roentgen therapy in active rheumatic heart disease. Their experience covered 48 patients observed during eleven and one-half years. The impression was gained that low grade infections respond better to irradiation than the more acute types and that patients with congestive failure are poor subjects for this form of therapy. Patients with cardiac pain are uniformly helped, save those with aortic regurgitation. The manner in which improvement is initiated is unknown. The technical method has been described. We feel, however, that it is difficult to judge the value of any such therapeutic measure on the basis of the rate of convalescence from a low grade rheumatic infection, which is so notoriously variable in its course.

BACTERIAL ENDOCARDITIS

Keefer⁶¹ has studied a group of 15 patients with active bacterial endocarditis but without bacteremia. There was no essential difference in the clinical course recorded for these patients and that for a comparable group of patients with bacteremia except that the nonbacteremic patients were more likely to have renal insufficiency as an outstanding feature of their illness. A significant parallel was drawn between the endocarditis in horses which have been immunized against pneumococci and the bacterial endocarditis of patients whose blood is sterile on culture. The high antibody titer in the horse blood favors the localization of bacteria but at the same time destroys bacteria released into the blood stream. Keefer has presented presumptive evidence that an analogous condition obtains in man.

Gross and Fried⁶² have described the macroscopic and microscopic appearance of the heart in 42 cases of subacute bacterial endocarditis and in 28 cases of acute bacterial endocarditis. Seventy-five per cent

58 Barnacle, C H, Ewalt, J R, and Ebaugh, F G. Artificial Fever Treatment of Chorea. A Two Year Study, *J A M A* **109** 111 (July 10) 1937.

59 Kendell, H W, and Simpson, W M. Artificial Fever Therapy of Sydenham's Chorea, *Ohio State M J* **33** 1097, 1937.

60 Levy, R L, and Golden, R. Roentgen Therapy of Active Rheumatic Heart Disease. A Summary of Eleven Years' Experience, *Am J M Sc* **194** 597, 1937.

61 Keefer, C S. Subacute Bacterial Endocarditis. Active Cases Without Bacteremia, *Ann Int Med* **11** 714, 1937.

62 Gross, L, and Fried, B M. The Role Played by Rheumatic Fever in the Implantation of Bacterial Endocarditis, *Am J Path* **13** 769, 1937.

of the hearts had been the seat of a rheumatic process, and Aschoff bodies were encountered in approximately 30 per cent. Reasons have been given which indicate that activity of a rheumatic infection is not a necessary precursor to the development of bacterial endocarditis, much more important are the formation of eosinophilic necrosis of the valvular closure line and the thrombotic, proliferative and necrotic changes at these sites. It did not appear to the authors that the vascularization occurring in rheumatic valves plays an appreciable role in the implantation of bacterial endocarditis.

Chester⁶³ has reported a case that is of unusual interest because it is the first recorded instance of apparent recovery from subacute bacterial endocarditis of a patient with patency of the ductus arteriosus.

ARTERIAL HYPERTENSION

Pathogenesis—It has been shown repeatedly that renal ischemia, produced by constricting the main renal arteries, as suggested by Goldblatt, will cause arterial hypertension. Experimental constriction of one renal artery results in temporary hypertension, and constriction of both results apparently in permanent hypertension. The amount of constriction determines the degree of hypertension. Thus slight constriction generally results in a benign form, usually without evidence of renal impairment, moderate or severe constriction results in a malignant form, with much renal impairment, and complete occlusion causes little or no rise in blood pressure. Many other methods which reduce the renal function and which have been recently tried⁶⁴ do not result in a permanent increase in blood pressure. Constriction of splenic and of femoral vessels has no effect on blood pressure.

The exact mechanism whereby the kidney produces the rise in blood pressure in experimental hypertension is still unsolved, although it is the immediate result of the narrowing of the arterioles, the blood volume, blood viscosity and cardiac output remain normal. The problem thus appears to be the same as it is in essential hypertension. It was at first thought that the nervous system might play an essential role, with the reflex stimulation coming from the ischemic kidney. However, this does not seem likely,⁶⁵ since denervation of the kidneys, section of

63 Chester, W. Patent Ductus Botalli with Subacute Bacterial Endocarditis and Recovery, *Am Heart J* **13** 492, 1937.

64 Scarff, R. W., and McGeorge, M. Experimental Renal Lesions and Blood Pressure in Rabbits, *Brit J Exper Path* **18** 59, 1937. Konzett, H., and Unna, K. Die Blutdruckänderungen nach Ausschalten von Nierenarterien an Hunden, *Arch f exper Path u Pharmakol* **186** 694, 1937.

65 Goldblatt, H., Gross, J., and Hanzel, R. F. Studies on Experimental Hypertension. II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, *J Exper Med* **65**:233, 1937. Goldblatt, H. Studies on

the anterior nerve roots, total sympathectomy and denervation of the heart combined with total sympathectomy do not abolish the hypertension. Furthermore, it has been shown⁶⁶ that constriction of the artery of a transplanted kidney, free from any possible nervous connections, leads to an increase in blood pressure.

The results of Goldblatt's⁶⁷ recent experiments, which were given in a preliminary report, suggested that the mechanism of this type of hypertension is primarily humoral and of renal origin. Thus, varying degrees of constriction of both main renal arteries are followed by hypertension while bilateral nephrectomy is not. This difference has been attributed to the absence of a hypothetic effective substance when the kidneys are absent. The constriction or occlusion of both renal arteries, when accompanied by occlusion of the renal veins, is not followed by the development of hypertension. This has been interpreted as being due to interference with the entrance of the hypothetic effective substance into the circulation. When hypertension is produced by constriction of one or both renal arteries, release of the constriction is followed, in a greater or lesser time, by return of the pressure to normal. Excision of the ischemic kidney at the height of the hypertension which follows constriction of one main renal artery is also followed by prompt return of the blood pressure to normal. It is interesting that Houssay, on the basis of transplantation of "ischemic kidneys," also concluded that the ischemic kidney secretes substances that cause permanent arterial hypertension.

Goldblatt⁶⁷ has also carried out various experiments on the effect of partial and complete adrenalectomy, with and without supportive and substitution therapy, which have indicated that the adrenal cortex, but not the medulla, may play a significant role in this type of hypertension. The manner in which the adrenal cortex acts in this regard is as yet

Experimental Hypertension. III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, *ibid* **65** 671, 1937. Goldblatt, H., and Wartman, W. B. Studies on Experimental Hypertension. VI. The Effect of Section of Anterior Spinal Nerve Roots on Experimental Hypertension Due to Renal Ischemia, *ibid* **66** 527, 1937. Freeman, N. E., and Page, I. H. Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, *Am Heart J* **14** 405, 1937. Dicker, E. Recherches sur la pathogenie de l'hypertension. II. Une lésion rénale peut déterminer une élévation de la pression sanguine, *Acta med Scandinav* **93** 265, 1937.

66 Blalock, A., and Levy, S. E. Studies on the Etiology of Renal Hypertension, *Ann Surg* **106** 826, 1937. Glenn, F., Child, C. G., and Heuer, G. J. Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney. Experimental Investigation, *ibid* **106** 848, 1937.

67 Goldblatt, H. Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann Int Med* **11** 69, 1937.

unknown, it may prepare the arteriolar musculature for the action of the hypothetic renal substance, or the reverse may be the case

Page and Sweet⁶⁸ produced hypertension in dogs by means of Goldblatt's clamp and then removed the hypophysis. This reduced the arterial pressure to levels slightly above normal. If then, the constriction of the renal arteries was increased, a transient rise in pressure resulted, a rise in pressure also resulted if the dogs were fed thyroid. It was concluded that the effect of hypophysectomy on hypertensive dogs is indirect and probably associated with a lack of secretion from the adrenal and thyroid glands.

Wollheim⁶⁹ has found a depressor substance in the urine of normal men and horses which differs from other depressor substances previously described. It is absent or present only in small amounts in the urine of patients with essential hypertension or with hypertension due to renal disease.

Two excellent papers⁷⁰ have appeared on hypertension associated with benign chromaffin cell tumors. A fairly definite clinical picture is usually observable in these cases.

Longcope⁷¹ has described his studies of 22 cases of chronic bilateral pyelonephritis. The clinical features of this disease, during its various stages, have been presented in some detail. Arterial hypertension was present in 10 of 15 patients who were observed during the terminal stages of the disease. The hypertension was not associated with pronounced or extensive arteriosclerosis in 9 fatal cases in which autopsy was performed. It was concluded that the explanation for the hypertension of pyelonephritis, occurring particularly during the latter stages of renal contraction, is not clear.

Butler⁷² has reported his observations on children with chronic pyelonephritis and arterial hypertension. The blood pressure of 1 of the patients with unilateral pyelonephritis and hypertension returned to normal after removal of the infected kidney.

68 Page, I. H., and Sweet, J. E. The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am J Physiol* **120** 238, 1937.

69 Wollheim, E. Eine neue körpereigene blutdrucksenkende Substanz und ihre Bedeutung für die essentielle Hypertonie, *Acta med Scandinav* **9** 1, 1937.

70 Howard, J. E., and Barker, W. H. Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Phaeochromocytomata), *Bull Johns Hopkins Hosp* **61** 371, 1937. Edward, D. G. F. Phaeochromocytomata and Hypertension, with Details of a Case, *J Path & Bact* **45** 391, 1937.

71 Longcope, W. T. Chronic Bilateral Pyelonephritis. Its Origin and Its Association with Hypertension, *Ann Int Med* **11** 149, 1937.

72 Butler, A. M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889, 1937.

Liston ⁷³ has reported interesting observations on 15 patients with food allergy in whom the ingestion of the offending foods caused a rise in blood pressure. Cure is effected simply by dietary regulation.

Shattuck ⁷⁴ has measured the blood pressure of over 400 pure Indian and Spanish-Indian natives of Guatemala. The systolic pressure averaged about 10 mm lower than that of North Americans living in the United States. Careful consideration of many factors suggested that the factors responsible for the lower systolic pressure of Guatemalans are racial characteristics, the slow tempo of life and a possibly deficient diet. The diastolic pressure of Guatemalans is nearer the standard for Americans in the United States than is the systolic pressure.

Hines ⁷⁵ has considered the hereditary factor in essential hypertension. He found that a family history of hypertensive cardiovascular disease is five times as frequent among persons who have hypertension or who are hyperreactors to a standard stimulus test (cold pressor test) as it is among persons who react normally to the test. In the study of twins and family groups he found that the type of reaction of the blood pressure to the test followed an inherited pattern. Because hyperreactors were not found who did not have at least one parent who had hypertension or was a hyperreactor, he concluded that it is probable that the trait is inherited as a dominant characteristic and that the hereditary factor plays an important role in the development of essential hypertension.

Signs and Symptoms—Two papers ⁷⁶ have appeared on the electrocardiogram with a chest lead in cases of arterial hypertension. The various abnormalities were described, and it was concluded that chest leads are often of value.

Holden ⁷⁷ found no evidence of a relation between blood pressure and cholesterol saturation of the plasma in a series which included patients with malignant hypertension, benign hypertension and chronic hemorrhagic nephritis. The plasma in all cases was approximately saturated with regard to free cholesterol, and the suggestion that supersaturation may exist was not substantiated.

73 Liston, O. Hypertension Caused by Food Allergy, *J Missouri M A* **34** 199, 1937.

74 Shattuck, G. C. The Possible Significance of Low Blood Pressures Observed in Guatemalans and in Yucatecans, *Am J Trop Med* **17** 513, 1937.

75 Hines, E. A. The Hereditary Factor in Essential Hypertension, *Ann Int Med* **11** 593, 1937.

76 van Nieuwenhuizen, C. I. C., and Hartog, H. A. T. The Electrocardiogram in Hypertension, with Especial Reference to Lead IV, *Am Heart J* **13** 308, 1937.
Roth, I. R. Chest Lead Tracings in Arterial Hypertension with Cardiac Enlargement, *ibid* **14** 155, 1937.

77 Holden, R. F., Jr. Plasma Cholesterol Saturation in Patients with Hypertension, with a Note on Preparation of Glass Filters for Micro-Filtration of Cholesterol Digonide, *J Clin Investigation* **16** 763, 1937.

Apperly and Cary⁷⁸ have shown that the increased chloride content of the blood of patients with arterial hypertension is wholly confined to the red blood cells

Treatment—The results of various operative procedures used in the treatment of arterial hypertension are, on the whole, not encouraging

Page and Heuer⁷⁹ have found that resection of splanchnic nerves, with interruption of the thoracic sympathetic chain, resulted in only a temporary fall of blood pressure in 9 cases. Subjective improvement occurred in 6, but in 3 of these the improvement lasted only a year. Renal efficiency was unaffected by the procedure. The same authors⁸⁰ reported their results in the treatment of 17 hypertensive patients by section of the anterior roots of the sixth dorsal to the second lumbar spinal nerves. Six patients had benign and 5 had malignant hypertension, the remaining 6 were young women with signs and symptoms of the "hypertensive diencephalic syndrome." Varying degrees of improvement occurred in all patients save 2 of the 5 with malignant hypertension. The favorable responses included a marked prolonged lowering of the arterial pressure, the remission of such symptoms as headache, pressure in the head and easy fatigability, and marked improvement in the disposition. There was a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most but not all the patients. Renal efficiency remained unchanged, despite the partial denervation of the kidneys which resulted from the operation or from the fall in blood pressure.

Freyberg and Peet⁸¹ have presented a report of interesting effects of splanchnicectomy on changes in the blood pressure and their relation to renal function. It is evident from their data that this procedure performed on patients with primary hypertension and normal renal function does not harm the kidneys or interfere with their functional efficiency. What is more important is that when hypertension is greatly relieved by splanchnicectomy, renal function that has previously been impaired improves and may even return to normal. This improvement has been declared both by an increase in concentrating ability and by an increase in urea clearance. It was concluded that the impairment of

78 Apperly, F. L., and Cary, M. K. Arterial Hypertension. The Site and Significance of the High Chloride Content of the Blood, *Am J M Sc* **194** 352, 1937

79 Page, I. H., and Heuer, G. J. The Effect of Splanchnic Nerve Resection on Patients Suffering from Hypertension, *Am J M Sc* **193** 820, 1937

80 Page, I. H., and Heuer, G. J. Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, *Arch Int Med* **59** 245 (Feb) 1937

81 Freyberg, R. H., and Peet, M. M. The Effect on the Kidney of Bilateral Splanchnicectomy in Patients with Hypertension, *J Clin Investigation* **16** 49, 1937

renal function is caused by vascular constriction and that if this constriction is relieved by splanchnicectomy, renal activity is benefited

Other papers⁸² have also appeared dealing with various operative procedures or their complications in the treatment of hypertension. From a review of all these studies it seems safe to conclude that section of the anterior nerve roots has given the best therapeutic results, although it is a serious operation, that partial removal of the normal adrenal glands is unsatisfactory and that improvement following the section of various nerves may be due to improved circulation through the kidneys as well as, or rather than, to simple denervation of a large vascular area. We believe, however, that there have not been adequate control studies, convalescence after any operation of course has a salutary effect on patients with hypertension.

Reports on various medical methods of treating hypertension have appeared, including salt restriction,⁸³ thiocyanate therapy,⁸⁴ the "class method"⁸⁵ and the effect of deep breathing.⁸⁶ All have indicated at least some degree of success.

HEART DISEASE DUE TO CORONARY ARTERIOSCLEROSIS

Glendy, Levine and White⁸⁷ have made an interesting study of coronary disease in youth, including a comparison of 100 patients with this disease under 40 years of age with 300 healthy persons past 80 years of age. Of the 100 young patients, the diagnosis of coronary

82 Hermann, H, and Sabadini, L. La resection des nerfs splanchniques est-elle légitime comme traitement de l'hypertension artérielle essentielle permanente? *Presse méd* **45** 41, 1937. Allen, E V, and Adson, A W. The Physiological Effects of Extensive Sympathectomy for Essential Hypertension, *Am Heart J* **14** 415, 1937. Craig, W M, and Adson, A W. Rationale of Surgical Treatment of Hypertension, *S Clin North America* **17** 1063, 1937. Donzelot, E, and Menetrel, B. La surrenalectomie dans les hypertensions artérielles, *Arch d mal du cœur* **30** 553, 1937. Lowenstein, W, and Weissmann, A. Zur Frage der Nierenstielenntnervung bei der Hypertension, *Wien med Wchnschr* **87** 675, 1937. Leriche, R. Des douleurs provoquées par l'excitation du bout central des grands splanchniques (douleurs cardiaques, douleurs pulmonaires) au cours des splanchnicotomies, *Presse med* **45** 971, 1937.

83 Steffen, H L. Zur Behandlung Kranker mit erhöhtem Blutdruck durch Kochsalzzug, *Deutsche med Wchnschr* **63** 90, 1937.

84 Griffith, J Q, Jr, and Lindauer, M A. Thiocyanate Therapy in Hypertension, Including a New Method for Determining Blood Thiocyanates, *Am Heart J* **14** 710, 1937.

85 Buck, R W. The Class Method in the Treatment of Essential Hypertension, *Ann Int Med* **11** 514, 1937.

86 Tirala, L G. Die Wirkung des Tiefatmens auf den Blutdruck, *Deutsche med Wchnschr* **63** 92, 1937.

87 Glendy, R E, Levine, S A, and White, P D. Coronary Disease in Youth. Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, *J A M A* **109** 1775 (Nov 27) 1937.

thrombosis was established clinically in 78, 70 had angina pectoris and 49 had both conditions. One patient had neither angina pectoris nor clinically evident coronary thrombosis but showed electrocardiographic evidence of serious coronary disease. The ratio of men to women was 24:1. Hypertension was found to be less common than in persons of all ages with coronary disease but was present in 3 of the 4 women in the group. The size of the heart was normal in over half the young patients, and, in general, the electrocardiographic observations were much the same as those for older patients. The prognosis of coronary disease in patients under 40 is considerably better than that in older patients, but much the same uncertainty exists.

Their summary of the prominent differences as to mode of life between the 100 young patients with coronary disease and the 300 healthy persons over 80 years of age was as follows:

Relatively far more (90 per cent) of the old folks than of the young group with coronary disease were of British stock, but here selection and other factors, such as time of immigration, may well enter. There were no persons of Jewish extraction in the older group, whereas 39 per cent of the young group were Jewish. Long-lived ancestors were more common to the aged group. However, it is of interest that the fathers of the younger group who died outlived the mothers by an average of five years. This relationship is usually reversed by several years. The majority of the old group have resided in small towns, villages or the country, in contrast to the young group, whose residence has been almost wholly urban. The younger group consisted largely of business or professional men. Among the old folks the occupations requiring physical activity were more common. A large number of the old group had exercised considerably to well beyond middle life. The young group were for the most part sedentary in habit and exercised very little.

The older group claimed to have eaten more moderately and perhaps more sparingly of such cholesterol-containing foods as milk and eggs. Tobacco was used in greater quantity and by a greater number in the young group, the incidence of smokers being 93 per cent, which exceeds even the high incidence in the general population. The use of alcohol differs less widely for the two groups. There were slightly more total abstainers in the old group and few heavy drinkers in either group. With rare exceptions a history of serious infections (e. g., smallpox, typhoid fever and malaria) was much more common in the older group. A greater proportion of the older group were exemplary in their sleeping habits, and fewer of them were constipated. Nearly 70 per cent of the young group were robust in build or distinctly fat, whereas 83 per cent of the old folks were of average build or had been thin and lean for most of their lives. Nervous sensitivity and strain were frequently encountered in the young group but practically negligible in the older group.

Davis and Blumgart⁸⁸ studied the relation of cardiac hypertrophy to coronary arteriosclerosis and congestive heart failure. They found

⁸⁸ Davis, D., and Blumgart, H. L. Cardiac Hypertrophy. Its Relation to Coronary Arteriosclerosis and Congestive Heart Failure, *Ann Int Med* **11** 1024, 1937.

that in patients with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy, while with more serious involvement a slight or moderate degree of hypertrophy is seen. When, in addition to coronary arteriosclerosis, the factor of congestive failure is added, the resulting cardiac hypertrophy is usually marked, the degree of cardiac hypertrophy seemed generally proportional to the severity and duration of congestive failure. They concluded that these results support the "injury theory" of the causation of cardiac hypertrophy rather than the widely held "work hypertrophy theory."

Snellen and Nauta⁸⁹ have emphasized that in the routine examination of the thorax roentgenographically it is often possible to detect calcification of the coronary arteries when this is present. It may well be that this method of diagnosing coronary arteriosclerosis will find wider application than it has thus far.

Gross and his associates⁹⁰ found that ligation of the coronary sinus in dogs was followed by considerable dilatation and widening of existing vascular channels on the surface of the heart and a conspicuous increase in the extent of the vascular bed. Subsequent occlusion of the left descending coronary branch was not followed by infarction in the majority of instances. It was further shown that partial occlusion of the coronary sinus, which is associated with a low operative mortality, appears to lower the mortality rate following sudden occlusion of the left anterior descending branch and to diminish the extent of the infarction. The possibility of applying this procedure to man was mentioned.

Blumgart and his co-workers⁹¹ have reported their experiments designed to learn whether temporary interruption of the blood supply to a portion of the heart results in persistent electrocardiographic or anatomic changes. Electrocardiographic changes were found to persist during the entire postoperative period (one to nine days) in all animals in which occlusion was maintained for from fifteen to forty minutes. When the period of occlusion was ten minutes or less, the electrocardiographic changes persisted in only 1 instance. Postmortem examinations did not reveal gross or histologic evidence of cardiac infarction in any instance. The clinical counterpart of these tests is suggested by

89 Snellen, H. A., and Nauta, J. H. Zur Röntgendiagnostik der Koronarverkalkungen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **56** 277, 1937.

90 Gross, L., Blum, L., and Silverman, G. Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, *J. Exper. Med.* **65** 91, 1937.

91 Blumgart, H. L., Hoff, H. E., Landowne, M., and Schlesinger, M. J. Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes, *Am. J. M. Sc.* **194** 493, 1937.

those patients with angina pectoris who show persistent electrocardiographic abnormalities and for whom postmortem examination reveals neither coronary occlusion nor myocardial infarction

Whitten⁹² has stated that the use of a midaxillary or lateral thoracic lead of the electrocardiogram in some cases appears to show earlier and to a more marked degree than the limb leads the electrocardiographic changes characteristic of infarction of the T_1 type. In not a single case did inversion of T_1 or T_2 or significant depression or elevation of RS- T_1 or RS- T_2 occur in the midaxillary lead unless there was definite reason to suspect cardiac damage, furthermore, in every instance of inversion of T_1 in the limb lead this degree of inversion was equaled or exceeded in the midaxillary lead. In the T_3 type of infarction, whether or not it is combined with the T_1 type, the limb lead provides a better record than the midaxillary lead.

Master, Dack and Jaffe,⁹³ and Kerr,⁹⁴ among others, have discussed various types of cardiac arrhythmia observed in cases of coronary thrombosis. Of the various arrhythmias, heart block alone appears to be associated with a specific anatomic lesion in the heart, namely, infarction of the posterior wall due to occlusion of the right coronary artery. Arrhythmia provoked by acute arterial occlusion is often ephemeral and remits spontaneously.

Wolferth⁹⁵ has written an excellent article which adequately expresses the present day clinical concepts of acute coronary occlusion. Master, Dack and Jaffe⁹⁶ have contributed an important study on factors and events associated with the onset of coronary thrombosis. The reasonable conclusion was reached that no known specific factor precipitates this thrombosis. Feil,⁹⁷ and Sampson and Eliaser⁹⁸ have emphasized the importance and have described the characteristics of attacks of precordial pain which may represent a precursory phenomenon of characteristic acute coronary occlusion.

92 Whitten, M. B. Midaxillary Leads of the Electrocardiogram in Myocardial Infarction, *Am Heart J* **13** 701, 1937

93 Master, A. M., Dack, S., and Jaffe, H. L. Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, *Ann Int Med* **11** 735, 1937

94 Kerr, J. D. O. Heart Block in Coronary Thrombosis, *Lancet* **2** 1066, 1937

95 Wolferth, C. C. Present Concepts of Acute Coronary Occlusion, *J A M A* **109** 1769 (Nov 27) 1937

96 Master, A. M., Dack, S., and Jaffe, H. L. Factors and Events Associated with Onset of Coronary Artery Thrombosis, *J A M A* **109** 546 (Aug 21) 1937

97 Feil, H. Preliminary Pain in Coronary Thrombosis, *Am J M Sc* **193** 42, 1937

98 Sampson, J. J., and Eliaser, M. The Diagnosis of Impending Acute Coronary Artery Occlusion, *Am Heart J* **13** 675, 1937

Blumer,⁹⁹ and Gravier and his associates¹⁰⁰ have commented on the importance of embolism as a complication of cardiac infarction. Intracardiac thrombi are present in about 50 per cent of the cases, and clinically recognizable embolic phenomena occur in about 14 per cent. Embolism is most likely to occur during the first ten days following cardiac infarction. Protracted rest and the avoidance of the use of digitalis, unless specially indicated, are important.

Palmer¹⁰¹ studied the prognosis, size of the heart and changes in the blood pressure following coronary thrombosis. He found that hypertensive patients have a somewhat more favorable outlook than nonhypertensive patients but that changes in the blood pressure and the height of the blood pressure after recovery from coronary thrombosis are of little significance. Cardiac enlargement is a most important factor in causing restriction of activity, and the prognosis for the patient with an enlarged heart and with congestive failure is slightly less favorable. He concluded that hypertension is by far the most important factor causing cardiac enlargement after coronary thrombosis. This is not in full agreement with the previously mentioned conclusion of Davis and Blumgart.⁸⁸

Angina Pectoris—There have been a number of worth while articles on various aspects of coronary heart disease and angina pectoris,¹⁰² but they will not be reviewed here.

99 Blumer, G. The Importance of Embolism as a Complication of Cardiac Infarction, *Ann Int Med* **11** 499, 1937.

100 Gravier, L., Tourniaire, A., and Bourret, M. Les embolies pulmonaires au cours de l'infarctus du myocarde, *Lyon med* **160** 357, 1937.

101 Palmer, J. H. The Prognosis Following Recovery from Coronary Thrombosis, with Special Reference to the Influence of Hypertension and Cardiac Enlargement, *Quart J Med* **6** 49, 1937, The Size of the Heart After Coronary Thrombosis, *Canad M A J* **36** 387, 1937, The Blood Pressure in the Years Following Recovery from Coronary Thrombosis, *Lancet* **1** 741, 1937.

102 Bourne, G., Scott, R. B., and Wittkower, E. The Psychological Factor in Cardiac Pain, *Lancet* **2** 609, 1937. Wittkower, E. The Psychological Factor in Cardiac Pain, *ibid* **2** 665, 1937. Bourne, G. Angina Innocens. Clinical Study, *Brit M J* **1** 695, 1937. White, P. D. The Criteria for the Diagnosis of Coronary Disease, *New England J Med* **217** 783, 1937. Riseman, J. E. F., and Brown, M. G. An Analysis of the Diagnostic Criteria of Angina Pectoris, *Am Heart J* **14** 331, 1937. Stalker, H. Angina Pectoris and Pernicious Anemia (Old Terminology). A Resume of the Literature, with a Case Report, *Ann Int Med* **10** 1172, 1937. Burnett, C. T. Pain and Pain Equivalents in Heart Disease, *ibid* **10** 1156, 1937. Boas, E. P., and Levy, H. Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris, with Special Reference to Shoulder Pain, *Am Heart J* **14** 540, 1937. Seymour, W. B., and Liebow, A. A. "Abdominal Intermittent Claudication" and Narrowing of the Celiac and Mesenteric Arteries, *Ann Int Med* **10** 1033, 1937.

The outstanding recent development in the treatment of angina pectoris concerns the possibility of substantially increasing the collateral coronary circulation by surgical means¹⁰³

Beck's operation consists principally of grafting vascularized fat and muscle on to the heart and sometimes placing powdered beef bone on the surface of the heart to produce a low grade inflammatory reaction. Thus far 25 patients with advanced coronary disease and angina pectoris have been operated on. Of these, 16 are living and 9 are dead, 8 of the deaths occurred within one week of the operation. Thirteen patients have been observed for five months or longer after the operation, 3 have improved greatly, 9 moderately and 1 slightly. The beneficial effect of the operation may be explained by an actual increase in arterial blood flow to the myocardium and a redistribution of blood that passes through the coronary arteries. The latter is brought about by opening up intercoronary communications by means of trauma, grafts and powdered bone placed on the surface of the heart. Beck concluded that the procedure is scientifically sound and that the results so far are encouraging. Although recognizing the interest and importance of this operative treatment, we wish to emphasize the natural tendency of spontaneous adjustment of the coronary circulation in many instances with no especial treatment at all.

O'Shaughnessy¹⁰⁴ has performed cardio-omentopexy on 5 patients with coronary heart disease. This operation consists in opening the chest by making an incision along the fifth intercostal space, incising the diaphragm and bringing a suitable portion of omentum into the thoracic cavity. The pericardium is incised, and the omentum is attached to the surface of the heart and to the edges of the pericardium. Six patients have submitted to this operation, 4 are much improved and 2 have died. The 2 deaths were not the result of operation but due to hemorrhage from a duodenal ulcer in one instance and uremia in the other. The results are encouraging indeed.

Love,¹⁰⁵ and Willius and Dry¹⁰⁶ have reported their results of the treatment of angina pectoris with trichlorethylene. Although the results were disappointing, it was suggested that this drug warrants a trial when the usual therapeutic agents fail to give relief.

103 Feil, H, and Beck, C S. The Treatment of Coronary Sclerosis and Angina Pectoris by Producing a New Blood Supply to the Heart, *J A M A* **109** 1781 (Nov 27) 1937. Mautz, F R, and Beck, C S. The Augmentation of Collateral Coronary Circulation by Operation, *J Thoracic Surg* **7** 113, 1937.

104 O'Shaughnessy, L. Surgical Treatment of Cardiac Ischaemia, *Lancet* **1** 185, 1937.

105 Love, W S, Jr. The Effectiveness of Trichlorethylene in Preventing Attacks of Angina Pectoris, *Ann Int Med* **10** 1187, 1937.

106 Willius, F A, and Dry, T J. Results from Trichlorethylene Inhalations in the Anginal Syndrome of Coronary Sclerosis, *Am Heart J* **14** 659, 1937.

Gold and his associates¹⁰⁷ studied the effect of theobromine and aminophylline on cardiac pain in a group of 100 patients with angina pectoris. Great care was taken to insure valid results, including the use of the so-called blind test and the alternate use of placebos and the xanthines. Their results showed that patients with cardiac pain are unable to distinguish between the effects of theobromine or aminophylline and those of a placebo. It was concluded, therefore, that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain. Laubry, Soulie and Laubry¹⁰⁸ similarly concluded that theophylline with ethylenediamine is of small value in the treatment of chronic coronary disorders.

Brown and Riseman,¹⁰⁹ however, concluded that definite improvement occurs in some patients with angina pectoris after the use of xanthines. By therapeutic test it was shown that the optimum dosage is usually the maximum amount that can be given without causing severe gastric distress and that the sodium acetate derivatives of theophylline and theobromine are the most effective preparations, the latter is much less expensive.

In connection with the foregoing observations concerning the effect of aminophylline in coronary disease, it is our clinical impression that patients who have advanced beyond the simple stage of angina pectoris to the state of myocardial weakness are most benefited by the drug. The benefit from the drug in such cases may be due in part to its diuretic effect and its stimulation of respiration.

MISCELLANEOUS CARDIAC DISORDERS

The Heart in Nutritional Deficiency States—For many years it has been known that cardiac enlargement and congestive failure may occur in beriberi. Recently Wenckebach and his associate Aalsmeer have greatly extended the knowledge of a group of disturbances of cardiac muscle in deficiency diseases, especially beriberi. During the past year several articles have appeared on this subject, the most notable being the contributions of Weiss and Wilkins¹¹⁰

107 Gold, H., Kwit, N. T., and Otto, H. The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain, *J. A. M. A.* **108** 2173 (June 26) 1937.

108 Laubry, C., Soulie, P., and Laubry, P. Action de la theophylline ethylene-diamine sur la circulation coronarienne, *Arch. d. mal. du cœur* **30** 256, 1937.

109 Brown, M. G., and Riseman, J. E. F. The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris, *J. A. M. A.* **109** 256 (July 24) 1937.

110 Weiss, S., and Wilkins, R. W. The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), *Ann. Int. Med.* **11** 104, 1937, Disturbances of the Cardiovascular System in Nutritional Deficiency, *J. A. M. A.*

These last named authors have shown that dysfunction of the cardiovascular system resulting from avitaminosis may occur in the United States and that in some respects the clinical picture resembles that of the classic "beriberi heart" observed in the Orient. Vitamin B deficiency plays the primary role in the precipitation of the disease. In the majority of cases there is moderate dilatation of the right ventricle, although the weight of the heart is not increased. The histologic changes in the myocardium include "hydropic" degeneration of the muscle and conductive fibers and increase in the intercellular substances, but the water content is unaltered. The signs and symptoms of the disorder do not form a rigid clinical syndrome, failure of the right or of the left ventricle, peripheral circulatory collapse and shock, singly or in combination, have been observed. The venous pressure is usually high, the arterial pressures normal and the blood velocity increased. The electrocardiograms in the great majority of cases reveal some abnormality. Digitalis is of no value, but vitamin B is a specific cure. These patients are seen mostly in the wards for alcoholic addicts of the large city hospitals and rarely in the other wards or in private practice.

The Heart After Diphtheria—Thompson, Golden and White¹¹¹ carefully studied 100 persons who had had severe or moderately severe diphtheria fifteen to twenty years previously. No clear instance of auriculoventricular or intraventricular block was found, and it was concluded that while there are acceptable cases of the development of disturbed conduction during the course of diphtheria and that in rare cases the disturbance persists permanently, there is as yet no proof that it may develop several years after the illness.

Blastomycosis of the Heart—Baker and Brian¹¹² have described 2 cases of generalized blastomycosis with cardiac involvement. No characteristic signs or symptoms of heart disease were discovered.

Cardiac Changes in Anemia Due to Hookworm—Porter¹¹³ has described certain physiologic adjustments to chronic anemia due to hookworm. Of particular interest was the cardiac enlargement which was found in every case studied. The data indicate that the change in

109 786 (Sept 4) 1937 Porter, W. B., and Higginbotham, U. The Heart in Endemic Pellagra, South M. J. **30** 1, 1937 Hashimoto, H. Acute Pernicious Form of Beriberi and Its Treatment by Intravenous Administration of Vitamin B, with Especial Reference to Electrocardiographic Changes, Am Heart J **13** 580, 1937

111 Thompson, W. P., Golden, S. E., and White, P. D. The Heart Fifteen to Twenty Years After Severe Diphtheria, Am Heart J **13** 534, 1937

112 Baker, R. D., and Brian, E. W. Blastomycosis of the Heart. Report of Two Cases, Am J Path **13** 139, 1937

113 Porter, W. B. Heart Changes and Physiologic Adjustment in Hookworm Anemia, Am Heart J **13** 550, 1937

cardiac size was in a few cases due to reducible dilatation, in others to dilatation and hypertrophy and in still others to definite hypertrophy unassociated with reducible dilatation. The primary cardiac dilatation may be classed as a physiologic adjustment mechanism which disappears when the anemia is relieved, yet if those factors which have necessitated the dilatation continue, there occurs hypertrophy of the myocardium which is not reducible and which is definitely pathologic.

Arteriovenous Fistula—Porter and Baker¹¹⁴ have studied in 4 patients the significance of cardiac enlargement caused by arteriovenous fistula. It was concluded that the increase in cardiac size is primarily an adjustment dilatation and that there is little hypertrophy present. This dilatation is not the result of decreased myocardial nutrition.

Cardiac Neurosis—White and Glendy¹¹⁵ have emphasized the growing importance of cardiac neurosis occasioned by the large amount of publicity accorded to heart disease. The early recognition and proper treatment in such cases may spare these subjects much time, money and suffering.

Trauma and Heart Disease—White and Glendy¹¹⁶ have written a comprehensive but concise report on trauma and heart disease. The general principles of the subject have been discussed, followed by consideration of etiologic relations, structural changes and functional derangements. Illustrative cases have been presented.

Aviation and Heart Disease—Graybiel and his associates¹¹⁷ described some effects of asphyxiation in patients with cardiac disease. Thirteen patients with heart disease and a like number of normal persons were subjected to an oxygen tension corresponding to an elevation of 14,500 feet (4.5 kilometers). The most striking feature of the test was the absence of complaint on the part of any subject, despite the fact that 3 of the patients fainted and 4 others exhibited signs of circulatory embarrassment. It was concluded that many patients with cardiac disease are endangered at high altitudes and that the untoward effects observed may be due to the general unfitness which is so often associated with heart disease or due more directly to embarrassment of the heart itself.

114 Porter, W. B., and Baker, J. P. The Significance of Cardiac Enlargement Caused by Arteriovenous Fistula, *Ann Int Med* **11** 370, 1937.

115 White, P. D., and Glendy, R. E. The Growing Importance of Cardiac Neurosis, *Ann Int Med* **10** 1624, 1937.

116 White, P. D., and Glendy, R. E., in Brahdv, L., and Kahn, S. Trauma and Disease, Philadelphia, Lea & Febiger, 1937, p. 24.

117 Graybiel, A., Missiuro, W., Dill, D. B., and Edwards, H. T. Experimentally Induced Asphyxiation in Cardiac Patients with Special Reference to Certain Hazards in Air Travel and to the Use of Asphyxiation as a Cardiac Functional Test, *J Aviation Med* **8** 3, 1937.

HEART FAILURE AND ITS TREATMENT

There have been a number of interesting articles¹¹⁸ bearing on the general subject of heart failure which cannot be reviewed because of considerations of space. Little advance has been made in regard to the treatment of congestive failure, although a few good reviews have appeared. Two volumes giving good résumés of the subject of congestive failure appeared in 1937, a small one by East¹¹⁹ and the other, a large volume by Fishberg,¹²⁰ which treated the various aspects of the subject in considerable detail.

Wood and his associate¹²¹ have used the term *trepopnea* to describe a phenomenon noted in certain cases of cardiac disease, namely, that the patient is comfortable in one recumbent position and uncomfortable in another recumbent position. This is probably due to a shift in position of the heart under the influence of gravity, which causes pressure

118 Greene, J. A., Paul, W. D., and Feller, A. E. The Action of Theophylline with Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, *J. A. M. A.* **109** 1712 (Nov 20) 1937. Marais, O. A. S., and McMichael, J. Theophylline-Ethylenediamine in Cheyne-Stokes Respiration, *Lancet* **2** 437, 1937. Cowan, J. H. Observations on Coramine, *Am. J. M. Sc.* **193** 673, 1937. Heim de Balsac, R. La théophylline éthylène-diamine (aminophylline) dans la pratique cardiovasculaire, *Paris med.* **2** 423, 1937. Thomson, W. A. R. The Organic Mercurial Diuretics in the Treatment of Cardiac Oedema, *Quart. J. Med.* **6** 321, 1937. Herrmann, G., and Decherd, G. M., Jr. Further Studies on the Mechanism of Diuresis, with Especial Reference to the Action of Some Newer Diuretics, *J. Lab. & Clin. Med.* **22** 767, 1937. Smith, F. M. Treatment of Left Ventricular Failure, *J. A. M. A.* **109** 646 (Aug 28) 1937. Stroud, W. D., and Vander Veer, J. B. A Six Year Study of the Clinical Efficacy of Various Digitalis Preparations, *ibid.* **109** 1808 (Nov 27) 1937. Moldavsky, L. F., and Visscher, M. B. The Energy Liberation at Constant Diastolic Fibre Length in the Tortoise Heart, with Particular Reference to the Effect of the Emptying Pressure, *J. Physiol.* **91** 23, 1937. Gibson, J. G., Jr., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, *J. Clin. Investigation* **16** 851, 1937. Thelen, A. Die venöse Blutstauung im Herzmuskel, *Virchows Arch. f. path. Anat.* **300** 243, 1937. Farber, S. Studies on Pulmonary Edema. I. The Consequences of Bilateral Cervical Vagotomy in the Rabbit, II. The Pathogenesis of Neuropathic Pulmonary Edema, *J. Exper. Med.* **66** 397, 1937. Burns, W., and Cruickshank, E. W. H. Changes in Creatine, Phosphagen and Adenylpyrophosphate in Relation to Gaseous Metabolism of the Heart, *J. Physiol.* **91** 314, 1937. Lewis, N. D. C. Psychic Phenomena in Association with Cardiac Failure, *Arch. Neurol. & Psychiat.* **37** 782 (April) 1937.

119 East, T. *Failure of the Heart and Circulation*, London, John Bale, Sons & Curnow, Ltd., 1937.

120 Fishberg, A. M. *Heart Failure*, Philadelphia, Lea & Febiger, 1937.

121 Wood, F. C., and Wolferth, C. C. The Tolerance of Certain Cardiac Patients for Various Recumbent Positions (*Trepopnea*), *Am. J. M. Sc.* **193** 354, 1937.

on certain mediastinal structures. The symptoms which force the patient to change position are usually dyspnea, precordial pain and cough. Most patients with trepopnea prefer lying on the right side and dislike lying on the left, but others have different preferences. In certain cases trepopnea is an etiologic factor in the production of paroxysmal nocturnal dyspnea.

Schmitkei and Levine¹²² have sought to explain the postdiuretic symptoms occasionally observed in digitalized patients. The transportation of a large amount of fluid from the body cavities and interstitial spaces through the body to the kidneys would expose the cardiovascular and nervous systems to the effect of any digitalis contained in this fluid. That such "redigitalization" is possible was shown by the discovery that body fluids from digitalized patients usually contained a significant amount of digitalis. It is conceivable that 0.5 Gm. or more of digitalis could be mobilized after marked diuresis—an amount which could provoke such symptoms as headache, giddiness, weakness, nausea and even vomiting. Further studies are necessary to substantiate the idea of digitalis intoxication with diuresis.

Macrez,¹²³ in an excellent article, has reviewed the subject of the use of opiates for patients with heart disease. Opiates have been out of favor several times in the past, the last time was shortly after Chai-cot died of acute pulmonary edema which was treated with morphine. At that time Huchard interdicted the use of morphine because of its supposedly depressing action on the heart and kidneys. Macrez, from the results of well authenticated animal and clinical investigations, has shown that opiates rarely have any untoward effect on the central nervous system, heart or kidneys but usually have a decidedly salutary effect. In regard to the dangers of habituation he has emphasized the fact that opiates are seldom needed over long periods by patients with cardiac disease save in terminal circumstances. A list of cardiovascular diseases in which opiates are indicated includes all those in which pain or dyspnea are prominent symptoms. The author concluded that there is scarcely a contraindication to their "lavish" use and that the risks are minimal.

The results¹²⁴ of total thyroidectomy in the treatment of heart disease are not gratifying. Apparently only a few patients with congestive failure are suitable for the operation. Patients with angina pectoris may often obtain symptomatic relief after total thyroidectomy, but a myxedematous state is not desirable and the operation carries considerable risk.

122 Schmitkei, M. A., and Levine, S. A. Presence of Digitalis in the Body Fluids of Digitalized Patients, *Arch. Int. Med.* **60**: 240 (Aug.) 1937.

123 Macrez, C. La morphine chez les cardiaques, *Paris med.* **2**: 221, 1937.

124 Parsons, W. H., and Purks, W. K. Total Thyroidectomy for Heart Disease, *Ann. Surg.* **105**: 722, 1937. Claiborne, T. S., and Hurxthal, L. Results of Total Thyroidectomy in Heart Disease, *New England J. Med.* **216**: 411, 1937.

News and Comment

Reprints of General Reviews—Requests have been received for annual reprints of the general reviews which since 1935 have been published in the ARCHIVES OF INTERNAL MEDICINE on allergy, diseases of metabolism and nutrition, the liver and biliary tract, diseases of the heart, blood, Bright's disease, infectious diseases, peripheral vascular diseases, gastroenterology, syphilis and neuropsychiatry. The type has been held, and if there is sufficient demand reprints of each year's reviews will be prepared.

Edward N. Gibbs Memorial Prize—It is announced by the New York Academy of Medicine, 2 East One Hundred and Third Street, New York, that a sum of approximately \$1,000 is available under the Edward N. Gibbs Memorial Prize toward original research in diseases of the kidney during 1938.

Candidates must be physicians who have been graduated at least three years and who are residents of the United States. They are requested to submit "evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney."

The award may be continued through not more than three years to any one person.

Applications with the required evidence should be addressed to the New York Academy of Medicine prior to June 1.

International Congress of Cosmobiology—The first International Congress of Cosmobiology will be held on the Côte d'Azur, June 2 to 6, 1938, under the auspices of the Société médicale de climatologie et d'hygiène du littoral Méditerranéen, with the collaboration of the Association internationale pour l'étude des radiations solaires, terrestres et cosmiques. Professor d'Arsonval, of the Institut de France, is chairman of the radiologic division, and A. Lumière, correspondent of the Academy of Sciences and Medicine, is chairman of the biologic division.

The program will include prehistory, protohistory and history of the knowledge of the action of the forces of the universe on terrestrial life, notions of astronomy and astrophysics, the solar corona and the periods of solar effervescence and their influence on crops, solar spectrum (ultraviolet and infra-red)—biologic, pathologic and therapeutic actions, other radiations emitted by the sun, undulatory or corpuscular rays called cosmic, high atmosphere and terrestrial magnetism, meteorology in its relations to morbid manifestations, on one hand, with atmospheric electricity and cosmic influences on the other, the constitution of microclimates and their utilization in medicine and botany, electric conductivity and ionization of the air—their eventual action on living beings, radioactivity of stone and soil—biologic, pathologic and therapeutic action, thermal and mineral waters.

Book Reviews

Klinische Elektrokardiographie mit einem Grundriss der Arrhythmien
By Dr Wilhelm Dressler Fourth edition Price, 10 50 marks Pp 180,
with 151 illustrations Berlin Urban & Schwarzenberg, 1937

This is a handbook of electrocardiography for the practicing physician without special training in this field of medicine. Professor Rothberger in an introductory note recommends the book for its usefulness to this group of physicians, more of whom, he believes, should employ the electrocardiograph. The conservatism in the evaluation of evidence of cardiac damage is indicated by the fact that the author does not mention the doubtfully significant minor changes, by his clear definition of normal variations, by his correlation of the electrocardiographic findings with clinical symptoms and signs and by his emphasis on the uncertainty of the prognostic value in the individual case. This conservatism is desirable because it should help the practicing physician avoid the usual mistakes of those inexperienced in this field.

The major part of the volume is concerned with the arrhythmias. Dressler recognizes the present predominant interest in the evidence of myocardial damage apart from the arrhythmias, but he believes that the detection of the presence and of the particular type of arrhythmia will always be an important function of the electrocardiogram. For each type of arrhythmia, in addition to the electrocardiographic findings the author presents a brief review of the pathologic physiology, symptoms, signs, diagnosis, prognosis and treatment. This clarifies and coordinates an otherwise puzzling subject.

The following are points of interest in regard to the electrocardiographic changes in cases of myocardial damage. Dressler rightly emphasizes the point that the general state of the myocardium is reflected chiefly in the RS-T interval and the T wave. He describes the type of electrocardiogram with hypertrophy of the left ventricle in which the RS-T segment in lead I is depressed and T wave inverted and states that this in itself is not evidence of myocardial damage in the usual sense. He believes that it may be caused partially by a disturbance in the excitatory pathway in the hypertrophied ventricle, thus having a mechanism somewhat similar to that of the electrocardiogram with oppositely directed QRS complexes and T waves seen in cases of defects of intraventricular conduction. He does not regard a Q_3 wave as significant unless Q_2 is also present. He believes that the precordial lead has definite limitations of usefulness in clinical diagnosis because it expresses changes chiefly in the myocardium directly underlying the electrode. He advises conservative evaluation of changes in the precordial lead, especially regarding the upright T wave. His statement that the Q_3 , T_3 type of electrocardiogram, indicating infarct of the posterior wall, carries a better prognosis than that indicating anterior infarction is controverted by other careful studies of this question.

In discussing the evidence of chronic myocardial damage the author mentions changes in the T wave and the RS-T segment in leads I and II but does not mention the equally significant although less frequent change seen in the second and third leads with acute and chronic strain of the right ventricle. He says that the temporary depression of the RS-T interval in leads I and II with corresponding changes in the T wave seen during an attack of angina pectoris may become permanent. Under figure 130 he describes an example of this in a case of syphilitic aortitis in which there were attacks of substernal pain. Since this type of electrocardiogram is so frequently seen in cases of strain of the left ventricle of various types and without necessarily the presence of disease of the coronary arteries, it is doubtful whether this should be considered evidence in the case cited and in other cases mentioned of disease of the coronary arteries.

The Avitaminoses The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases By Walter H Eddy, Ph D, and Gilbert Dalldorf, M D Price, \$4 50 Pp 338, with 32 illustrations Baltimore Williams & Wilkins Company, 1937

This book is described as a derivation from "The Vitamine Manual," which was written by the senior author fifteen years ago It is divided into two parts Part 1 considers the vitamins and the avitaminoses It deals with the nature and functions of the important vitamins, together with the clinical aspects and anatomic manifestations of their deficiency Part 2 is devoted to methods of assaying sources of vitamins, clinical tests of the deficiencies and a table of the vitamin values of foods

The chapters on vitamin A bring together much new information The two mechanisms of the production of ocular changes are clearly outlined, and the development of the widespread lesions of vitamin A deficiency are explained The chapters on the subclinical forms of avitaminosis A, B and C are particularly important in that they emphasize the little known fact that mild deficiencies are prevalent and may produce only nonspecific symptoms and signs Clinical indications of their presence may in many instances lead to verification by special procedures The discussion of the pellagra problem is highly colored by the beliefs of the authors However, the present status of the flavins is clarified The section on pellagra and that on vitamin E demonstrate an important weakness found throughout the book Controversial information is given without adequate discussion Facts and observations of other investigators are often merely listed Correlation and interpretation may be lacking where they are most needed by the physician, and elsewhere dogmatism is manifest regarding an equally controversial topic

The last three chapters concern methods of vitamin bioassay, clinical tests and the vitamin values of foods The descriptions of methods of assay and of clinical tests are brief but adequate for an understanding of the principles employed The table of the vitamin values of foods is expressed in international units per ounce Such figures are particularly helpful in a comparison of specific foods for their vitamin content and permit an estimation of the adequacy of vitamins in ordinary servings

The book contains not only many typographic errors, omission and transposition of letters but errors as to references, such as that to Wald on page 34 However, much information is given that is not available elsewhere under one cover

Concepts and Problems of Psychotherapy By Leland E Hinsie M D, Professor of Clinical Psychiatry, College of Physicians and Surgeons, Columbia University Assistant Director, New York State Psychiatric Institute and Hospital Preface by Nolan D C Lewis, Neurological Institute of New York Price \$2 75 Pp 199, with 1 chart and 5 tables New York Columbia University Press, 1937

Considering the numerous semipopular treatises written today, chiefly representing unhappy attempts to clarify the theories of Freud, it is a pleasant surprise to find a clear, concise though greatly abridged study of four modern methods of psychiatric therapy In the first 154 pages of his book Hinsie attempts to present and evaluate these four concepts of psychotherapy, namely (1) the psychoanalysis of Freud, (2) the psychobiology of Meyer, (3) the individual psychology of Adler and (4) the analytic psychology of Jung The major portion of the book is devoted to Freud's theories, many of which are simplified and explained for the benefit of the reader The author gives favorable and unfavorable criticisms of each method of psychotherapy that he presents, based on his own clinical experience and on data from numerous other sources

There is a chapter on the statistical evaluation of psychotherapeutic methods by Dr Carney Landis, who admits that at present statistical methods applied to therapeutic results in mental disease are hindered because the essential nature and

cause of the disease are unknown in the majority of cases, there is often disagreement of opinion among those qualified to know regarding the diagnosis and there is no uniformity of opinion with respect to usage of such terms as cured, recovered and improved, as applied in psychopathologic cases. Hinsie pleads for a greater application of statistical methods to psychotherapeutic procedures in order to make better evaluation possible. He presents data showing how statistics have resulted in aiding and developing methods of therapy in other special medical fields.

Undoubtedly students and specialists in the various branches of psychotherapy will criticize Hinsie's book for its brevity in their particular fields. However, there is no question that the book will serve as an excellent textbook for beginners in psychiatry and for those physicians in other special medical fields or in general practice who would like to gain some insight into modern psychotherapy.

Biological and Clinical Chemistry By Matthew Steel, Ph.D. Price, \$8
Pp 770, with 21 illustrations Philadelphia Lea & Febiger, 1937

This is a new textbook of physiologic chemistry, written expressly for medical students. It is intended to be used both as a classroom textbook and as a laboratory manual. In fulfillment of the latter aim, 268 experiments are described, which provide a comprehensive laboratory course. These are clearly outlined and are in the modern manner, in that the student is expected to use himself and his fellows for testing as often as he uses animals and chemicals.

The didactic portions, however, are subdivided in an unusual manner as regards emphasis on different phases of biochemistry. For example, 103 pages are devoted to physical chemistry and the biophysics of cells and tissues, 109 pages, to biochemical catalysts (enzymes), vitamins and hormones, 75 pages, to the chemistry of the blood, of which 28 are devoted to methods and experiments, and 48 pages, to the urine and the excretory process, of which about one third contain experiments. Nutrition, energy metabolism and carbohydrate metabolism are discussed in considerably less than 50 pages each. The physicochemical material and the organic chemistry (carbohydrates, lipids and proteins) are well described, even though one questions the necessity of some of the biophysics in a medical curriculum. On the other hand, the intermediate metabolism, in general, is presented superficially. The presentation of the acid-base balance is inadequate, and many recent contributions to human biochemistry are neglected.

The general tone of the clinical correlations may be detected from this excerpt from page 675:

"Since a man should consume 300 to 400 grams of glucose, or its equivalent in carbohydrate, a very severe diabetic will require *150 to 200* [italics not in text] units of insulin daily distributed in doses of 30 to 40 units five times a day."

There are many errors throughout, not all of which are typographic. Some proper names are rendered in a variety of ways, but the most startling is the designation of the late great nutritionist as Graham Lust (page 607).

Each chapter is terminated by a short but apparently satisfactory list of special and general references.

Cirurgia das glandulas parathyroides, anatomia cirurgica, tecnica indicacões, modo de acção By Sardinha Xavier da Silveira Pp 105, with 34 illustrations Rio de Janeiro, 1936

This monograph on the parathyroid glands consists chiefly of a review of the literature. In addition to a historical account of surgery of the parathyroid glands, the author and her co-workers have reviewed the reports of 1,052 cases in the literature, consisting of studies of cadavers, as to the variations in number, location and blood supply of the parathyroid glands. Seventy per cent of the patients were found to have the normal number—four. Less than four were found in 28 per cent. Anomalies of location were observed in 15 per cent.

The review of calcium metabolism and surgical technic presents no new findings. The discussion of parathyroidectomy for scleroderma and thrombo-angitis obliterans presents several interesting aspects. The author reports continued improvement after one year in a patient with scleroderma, a Brazilian woman who underwent parathyroidectomy.

The observations in the single case of scleroderma, according to the author, confirmed the findings of Leriche, Jung and Sureyya, Seyle, Shelling, Ashes and Jackson on the interrelation of scleroderma and parathyroid dysfunction. Leriche found that 70 per cent of the patients with scleroderma had hypercalcemia. Hypercalcemia was also observed in the case reported on by the author.

Three patients with thrombo-angitis obliterans treated by parathyroidectomy are reported on. Illustrations of the improvement in the lesions of the extremities accompany the discussion. Increased vasodilatation, increased temperature of the extremities, diminished pain and a lowered calcium level of the blood were some of the effects observed. These findings confirm, according to the author, those of Welti, of Paris, who has previously reported the use of parathyroidectomy as a therapeutic procedure in Buerger's disease. The condition is attributed to hypertonia of the sympathetic nervous system due to hypercalcemia.

Lehrbuch der Elektrokardiographie By David Scherf, M.D. Second edition. Price, 18 marks. Pp 264, with 186 illustrations. Vienna. Julius Springer, 1937.

This book represents a systematic approach to the understanding of electrocardiography in health and disease. It is simply written, and the electrocardiographic changes are described so that the beginner may gain an understanding of them with only a general background of cardiologic training. The outline is much the same as that in similar textbooks. The physiology of impulse conduction and the development of the electrical potential lead up to a consideration of the principles of the recording unit, a résumé of the anatomy and physiology of the specific myocardium and then a discussion of normal and abnormal electrocardiograms. The newer advances in electrocardiography are given. Both nomenclatures for bundle branch block are outlined. Thoracic leads are discussed. The differentiation of the curves in cases of pericarditis and coronary thrombosis is clearly given, and the confusion with pulmonary embolus is pointed out. A discussion of the bundle of Kent is included.

The second edition of this textbook has followed the first after only eight months. The reviewer has not seen the first edition, but, according to the author's statement, in the second edition the contents have been enlarged, and the newer literature has been taken into consideration.

A bibliography is appended to each section.

Les gastropathies des syphilitiques By Carlos Bonanno Udaondo. Preface by Émile Sergent. Paper. Price, 32 francs. Pp 216, with 19 illustrations. Paris. Masson & Cie, 1936.

This is a well written monograph dealing with syphilitic lesions of the stomach. Little original work is presented, but the subject is extensively reviewed. The bibliography contains 537 references. The author clearly states that his purpose in preparing the review was to clarify some of the more important diagnostic points of gastric syphilis and not to emphasize the occurrence of such lesions. Collecting data reported by twenty-three writers since the publication of Chiari's report in 1885, he compares the relative incidence of proved syphilitic lesions of the stomach according to (1) the incidence with regard to other gastric conditions, (2) the incidence in known syphilitic patients, and (3) the postmortem incidence of syphilis of the stomach. The author reviewed the various available classifications of gastric lesions of syphilitic origin and presents a simple but complete original classification, which should prove of merit. The major portion

of the monograph deals with the anatomic, roentgenographic laboratory and clinical findings of diagnostic value for each of the entities according to his classification. The material and method of presentation should prove of interest to those who are desirous of a fairly concise readable review of the subject.

Atlas of Hematology By Edwin E. Osgood, M.D., Assistant Professor of Medicine and Head of Experimental Medicine, University of Oregon Medical School, Portland, Ore., and Clarice M. Ashworth, Medical Illustrator, University of Oregon Medical School, Portland, Ore. Cloth. Price, \$10. Pp. 255, with 326 illustrations in color. San Francisco: J. W. Stacy, Inc., 1937.

An atlas is defined as "a volume of plates illustrating any subject." Judged by this definition, this atlas of hematology generously fulfils the requirements.

The book is divided into two general sections. The first part illustrates the various cells that may be found in the circulating blood and in the marrow and includes a description of the parasites which infest the blood. The second part deals with the diseases that are accompanied with characteristic changes in the blood picture. The diseases are dealt with in a somewhat abbreviated fashion as the book does not purport to be a treatise on diseases of the blood. It is offered to those who wish to gain proficiency in recognizing the cells that appear in the blood and marrow in normal and all pathologic conditions. To this end the book leaves little to be desired.

The cells are exceedingly well reproduced, and the color photography is excellent.

The authors describe a simple method by means of which any one with the most elementary knowledge of the subject should be able to identify almost any cell to be found on a well stained slide, even if he has never before seen such a cell. The book is characterized by its simplicity, and simplicity is always a sign of complete familiarity with the subject in hand.

There is a short chapter on laboratory methods, including the authors' technic for sternal puncture, and there is an excellent bibliography.

To the hematologist the book may appear elementary, but good hematologists are not numerous. For clinicians, students and technicians, to whom the book is primarily offered, it will most adequately perform its allotted task.

It is rather unfortunate that the authors have thought it advisable to propose a new nomenclature. The old established nomenclature has served a good purpose for a long time, and while the new terms offered in this work may be pleasing to the philologist, they are likely to be confusing to the clinician and student.

Christian R. Holmes, Man and Physician By Martin Fischer. Price, \$4. Pp. 233. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This presentation of the life of Dr. Christian R. Holmes includes a short discussion of his childhood, adolescent and college years and a more complete dissertation on his professional years. Fischer includes a detailed survey of Holmes' contributions to the medical development of Cincinnati. His ceaseless work in collecting funds, municipal grants and endowments for the construction, furnishing and adequate staffing of the Cincinnati General Hospital and Cincinnati Medical School is outstanding. His untiring aggressiveness was responsible for his success in achieving the desired ends, in spite of the corrupt political situation that existed in the city at that time. The book includes not only biographic material but a great deal of interesting historical information concerning the medical and political life of Cincinnati.

The book is well planned and lucidly and interestingly written. The large print on dull-finished paper is welcomed. Many proverbial remarks and the few illustrations that supplement the main presentation add to the value of the book.

This biography of Holmes offers enjoyable and instructive reading material concerning a man of whom the members of the medical profession and the laymen not only of Cincinnati but of America should be proud.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

IX BLOOD PLASMA PROTEIN VALUES FOR CONTROL AND PARTIALLY NEPHRECTOMIZED RATS FED DIETS CON- TAINING DRIED EXTRACTED BEEF MUSCLE

STEPHAN LUDEWIG, PH D

AND

ALFRED CHANUTIN, PH D

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Hypoproteinemia may follow excessive loss or deprivation of protein. Experimental hypoproteinemia has been produced by plasmapheresis and with diets low in protein. In man, hypoproteinemia is encountered after continued loss of protein in urine or during periods of dietary restriction of protein. Many investigators believe that the hypoproteinemia is entirely due to this loss of protein. However, in a recent discussion of the problem, Bloomfield¹ suggested "Part at least of the difficulty which leads to the lowering of the blood-proteins is an impairment of the blood-regenerating mechanism, lack and loss undoubtedly contribute an added burden which on occasion may be insuperable, but lack and loss clearly fail to explain the whole problem."

In the present investigation, control and partially nephrectomized rats fed diets containing varying amounts of dried extracted beef muscle were used in studying the relation between the plasma protein content and the amount of protein ingested and excreted. The partially nephrectomized rat is peculiarly suitable for such a study for the following reasons: 1 The urinary protein is chiefly albumin in proportions found in nephrotic urine of man. 2 The severity of the proteinuria increases with time. 3 The amount of dietary protein influences the excretion of protein to a certain extent. Despite the marked loss of protein by partially nephrectomized rats, neither hypoproteinemia nor visible edema was encountered.

From the Laboratory of Physiological Chemistry, the University of Virginia.

This investigation was made possible by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1 Bloomfield, A. L. The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J. Exper. Med.* **57**: 705, 1933.

METHODS

The operative procedure for unilateral and subtotal nephrectomy and the care of the experimental animals have been described.² The diets are presented in table 1. The control and partially nephrectomized rats were fed the experimental diets for periods ranging from seventy-five to one hundred and fifty days, with about one hundred days for the majority of animals.

Blood for analysis of protein was drawn from the abdominal aorta with needle and syringe while the animal was under light ether anesthesia. Potassium oxalate was used as the anticoagulant. An effort was made to use uniform concentration of potassium oxalate in order to minimize the analytic error pointed out by Peters, Eisenman and Bulger.³ The procedure described by Weech, Snelling and Goetsch⁴ was followed for the determination of total plasma, albumin and fibrin nitrogen. Globulin was precipitated with 22.2 per cent solution of sodium sulfate after incubation overnight, and the solution was filtered through a Whatman no. 50 filter paper. Fibrin was prepared for analysis according to the Cullen and Van Slyke⁵ method from 1 cc. of plasma. The micro-Kjeldahl apparatus was similar to Goebel's apparatus, described by Peters and Van Slyke.⁶ The nonprotein nitrogen content was determined by the procedure suggested by Daly.⁷ The blood

TABLE 1—Composition of Rations

Diet	Dried Extracted Beef Muscle	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture
EB 10	10	62	14	5	5	4
EB 20	20	52	14	5	5	4
EB 40	40	32	14	5	5	4
EB 60	60	12	14	5	5	4
EB 80	80		6	5	5	4

filtrate was prepared in a centrifuge tube by adding 0.2 cc. of plasma to 5 cc. of 2.5 per cent trichloro-acetic acid. Slightly more than 3 cc. of plasma was necessary for the determination of total plasma protein, albumin, globulin and nonprotein nitrogen. Since sufficient plasma was not always available to include analysis of fibrin, this determination alone was made for a number of other animals to obtain sufficient data. The urinary protein content was determined for urine collected during a concentration test according to the procedure of Folin.⁸

2 Chanutin, A. and Ferris, E. B., Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I. Control Diet, *Arch. Int. Med.* **49**: 767 (May) 1932.

3 Peters, J. P., Eisenman, A. J., and Bulger, H. A. The Plasma Proteins in Relation to Blood Hydration. I. In Normal Individuals and in Miscellaneous Conditions, *J. Clin. Investigation* **1**: 435, 1925.

4 Weech, A. A., Snelling, C. E., and Goetsch, E. The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, *J. Clin. Investigation* **12**: 193, 1933.

5 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 697.

6 Peters and Van Slyke,⁵ p. 530.

7 Daly, C. A. The Determination of Non-Protein Nitrogen with Special Reference to the Koch-McMeekin Method, *J. Lab. & Clin. Med.* **18**: 1279, 1933.

8 Folin, O. A Laboratory Manual of Biological Chemistry, New York, D. Appleton and Company, 1926, p. 210.

The standard error of the mean and the coefficient for reliability between two means were determined according to formulas recommended by Garrett⁹

RESULTS

Plasma Protein Values for Control Animals (One or Two Kidneys)

—The total protein, albumin and globulin nitrogen concentrations were determined for 97 control animals fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted beef muscle. The average values with their standard errors are presented in the first portion of table 2. The respective mean values for the total plasma protein and albumin were practically the same with the first four diets, but there was a statistically significant difference for these constituents for the groups fed the

TABLE 2—*Plasma Protein Values for Control and Partially Nephrectomized Rats*

No of Rats	Protein in Diet, %	Total		Albumin		Globulin		Fibrin*	
		Nitrogen, Mg per 100 Cc	Protein, Gm per 100 Cc	Nitrogen, Mg per 100 Cc	Protein, Gm per 100 Cc	Nitrogen, Mg per 100 Cc	Protein, Gm per 100 Cc	Nitrogen, Mg per 100 Cc	Protein, Gm per 100 Cc
Control Rats									
17	10	1,001 ± 10.7	6.25	562 ± 9.3	3.51	439 ± 15.8	2.74	44 ± 1.6	0.28 (18)
14	20	995 ± 14.3	6.23	552 ± 12.0	3.45	443 ± 9.4	2.77	47 ± 1.3	0.29 (26)
14	40	988 ± 11.1	6.17	531 ± 8.3	3.32	457 ± 12.8	2.86	45 ± 2.5	0.28 (19)
21	60	1,000 ± 15.3	6.25	550 ± 6.3	3.44	450 ± 13.1	2.82	42 ± 1.4	0.26 (21)
31	80	952 ± 9.4	5.95	505 ± 5.8	3.16	447 ± 9.9	2.80	46 ± 1.9	0.29 (12)
Partially Nephrectomized Rats									
38	10	988 ± 16.4	6.17	522 ± 13.4	3.26	466 ± 17.7	2.91	46 ± 2.0	0.29 (24)
24	20	938 ± 19.2	5.86	503 ± 13.1	3.14	435 ± 15.5	2.72	50 ± 2.5	0.31 (19)
19	40	935 ± 12.0	5.84	465 ± 11.5	2.91	470 ± 13.4	2.94	59 ± 3.0	0.37 (20)
24	60	955 ± 14.6	5.97	478 ± 11.6	2.99	477 ± 12.0	2.98	52 ± 3.2	0.33 (18)
26	80	928 ± 13.8	5.80	457 ± 11.3	2.86	471 ± 18.8	2.94	70 ± 3.6	0.44 (30)

* The figures in parentheses represent the number of rats used for determinations of fibrin

EB 80 diet. The average globulin and fibrin values were all within a small limited range with all diets and were without any statistically significant differences.

Since the mean values for the groups fed diets EB 10, EB 20, EB 40 and EB 60 were statistically reliable, they were combined with maximum and minimum values to establish standards for control rats fed well balanced diets (table 3).

Plasma Protein Values for Partially Nephrectomized Rats—The total plasma protein, albumin and globulin nitrogen concentrations were determined for 133 partially nephrectomized rats fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted beef muscle. The statistical

⁹ Garrett, H. E. *Statistics in Psychology and Education*, New York, Longmans, Green & Co., 1930.

analysis of the average values for each dietary group is presented in the second portion of table 2. There was a tendency for the concentrations of total plasma protein and albumin to decrease slightly as the protein concentration of the diet was increased. There was a statistically significant difference between the total plasma protein content with diet EB 10 and the values with the remaining diets. There was a significant difference between the albumin values with diets EB 10 and EB 20, respectively, and the values with diets EB 40, EB 60 and EB 80, respectively. There was no significant difference between the globulin values, despite the fact that the spread about the mean was greatest for this constituent. The maximum and minimum values for the various plasma constituents were as follows: total protein nitrogen, 1,192 and 800 mg

TABLE 3—*Plasma Protein Values for Control Rats*

Number of Rats		Mg of Nitrogen in 100 Cc of Plasma	Gm of Protein in 100 Cc of Plasma
66	Total	Maximum 1,180	
		Minimum 860	
		Mean $1,001 \pm 7.0$	6.25
	Albumin	Maximum 653	
		Minimum 465	
		Mean 548 ± 4.6	3.42
	Globulin	Maximum 592	
		Minimum 278	
		Mean 453 ± 6.6	2.83
	$\frac{\text{Albumin}}{\text{Globulin}}$ ratio = 1.21		
	Correlation coefficient between albumin and globulin = -0.14 ± 0.03		
96	Fibrin	Maximum 0.069	
		Minimum 0.029	
		Mean 0.045 ± 9.0	0.25

per hundred cubic centimeters, albumin nitrogen, 668 and 320 mg per hundred cubic centimeters, and globulin nitrogen, 757 and 257 mg per hundred cubic centimeters.

The average values for fibrin showed an increase in concentration with increased ingestion of protein. It should be noted that these increased values were not sufficient to influence the globulin values appreciably. The maximum and minimum variations for fibrin nitrogen for the partially nephrectomized rats were 106 and 28 mg per hundred cubic centimeters, respectively.

Comparison of Plasma Protein Values for Control and Partially Nephrectomized Rats—The data for the total plasma protein, albumin and globulin were statistically analyzed to determine the effect of partial nephrectomy for the respective dietary groups. It was found that there was no significant difference in the average values for total nitrogen for the groups of animals fed diets EB 10 and EB 80, but there was a significant difference for the groups fed diets EB 20, EB 40 and

EB 60 There was a significant difference between the average albumin values for all the respective dietary groups On the other hand, there was no significant difference in the average globulin values for the various dietary groups The values for fibrin were significantly greater for the partially nephrectomized animals fed diets EB 40, EB 60 and EB 80 than for the corresponding control groups It should be emphasized that the absolute decrease in the values for total plasma protein and albumin was not physiologically significant

Relation of Plasma Protein Values to Urinary Protein Values for Partially Nephrectomized Rats—In order to determine whether the concentration of plasma protein was related to the amount of protein excreted, all data were assembled under arbitrary ranges of proteinuria according to the amount of protein excreted in twenty-four hours, as follows group 1 (slight proteinuria), between 0 and 50 mg, group 2 (moderate proteinuria), between 50 and 100 mg, and group 3 (marked

TABLE 4—*Relation of Proteinuria to Plasma Protein Values for Partially Nephrectomized Rats*

Group	Number of Rats	Mg of Protein Excreted in 24 Hr *	Gm of Protein in 100 Cc of Plasma		
			Total	Albumin	Globulin
1	38	0-50 (28)	6.13 \pm 0.24	3.17 \pm 0.33	2.93 \pm 0.45
2	28	50-100 (72)	5.91 \pm 0.41	3.03 \pm 0.33	2.89 \pm 0.37
3	37	100-250 (145)	5.75 \pm 0.36	2.93 \pm 0.38	2.82 \pm 0.40

* The figures in parentheses represent averages

or massive proteinuria), between 100 and 250 mg The average values for plasma protein, albumin and globulin are classified according to the proteinuria in table 4

Since the differences in the concentration of the plasma protein for the respective groups were comparatively small, statistical analyses for the significance of the differences of the averages were carried out It was found that the average values for total plasma protein for groups 2 and 3 were definitely lower than the average value for group 1 There was a significant difference between the albumin values for group 1 and those for group 3 There were no appreciable differences in the globulin values for the three groups Although there were statistically significant differences between the groups with regard to the total plasma protein and albumin values, it can be seen that the plasma protein concentration was not sufficiently lowered to exert any untoward physiologic effect

The quantity of circulating plasma protein in 101 partially nephrectomized rats which was estimated from the total plasma protein con-

centration and the plasma volume (method of Cutting and Cutter¹⁰), was compared with the urinary protein excreted during a twenty-four hour concentration test. Thirty per cent of these animals excreted more than 50 per cent of the calculated total plasma protein in twenty-four hours. In two instances the twenty-four hour urinary excretion of protein was in excess of the calculated total plasma protein content. In the absence of hypoproteinemia this demonstrated a remarkable ability of the partially nephrectomized rat to regenerate plasma protein.

COMMENT

These experiments demonstrate that tremendous increases in the protein concentration of an adequate diet do not increase the plasma protein content for control and partially nephrectomized rats. Furthermore, the loss of relatively large quantities of urinary protein by partially nephrectomized rats has no appreciable effect on the concentration of plasma protein. This appears to be direct experimental evidence to support Bloomfield's suggestion that loss of urinary protein in renal disease does not satisfactorily explain the phenomenon of hypoproteinemia.

In the partially nephrectomized rat the renal tissue is reduced without directly affecting any other organ, but the degenerative and inflammatory nephropathies of man usually involve not only the kidney but other organs as well. If an analogy can be drawn between the response of man and that of the rat to the loss of urinary protein, it may be assumed that hypoproteinemia in man must be due to interference with the protein-regenerating mechanism. It seems likely that human plasma protein values cannot be elevated with high protein diets and that lowered plasma protein values for human beings with nephrosis must be attributed to altered protein regeneration rather than to proteinuria.

SUMMARY

The concentrations of plasma protein were determined for large numbers of individual control rats fed diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted beef muscle. The results obtained with the first four diets were almost identical and yielded the following averages: total plasma protein, 6.25 Gm, albumin, 3.42 Gm, globulin, 2.83 Gm, and fibrin, 0.28 Gm, per hundred cubic centimeters. The total plasma protein and albumin concentrations for the partially nephrectomized rats were slightly lower, and the fibrin values were slightly higher than these figures, except with diet EB 10,

¹⁰ Cutting, W. C., and Cutter, R. D. Total Plasma Protein in Normal and Fasting Rats, *Am J Physiol* **113** 150, 1935.

which produced control values. Hypoproteinemia was not encountered in any of these animals.

A comparison of the plasma protein concentrations for partially nephrectomized rats with the amount of protein excreted indicated that there was no decrease of physiologic importance in the total plasma protein and albumin values with increased proteinuria.

It was shown that the partially nephrectomized rat may excrete urinary protein during twenty-four hours in amounts as great as the total circulating plasma protein without evidence of hypoproteinemia.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

A BLOOD PLASMA CHOLESTEROL AND PHOSPHOLIPID PHOSPHORUS
VALUES FOR CONTROL AND PARTIALLY NEPHRECTOMIZED RATS
FED DIETS CONTAINING DRIED EXTRACTED LIVER

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AND

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Cholesterol metabolism in renal diseases has been reviewed by Cantarow¹ and by Page and his associates² The probable significance of phospholipids and their relation to free cholesterol have been discussed by Sinclair³ It is well known that there is an increased concentration of plasma cholesterol in nephrosis and in the nephrotic types of glomerulonephritis There appears to be no logical explanation for the changes in the cholesterol values of the blood in these diseases There has been little work concerning lipid metabolism of experimental animals with renal insufficiency to compare with results obtained for patients with impaired renal function

It is the purpose of this investigation to study the plasma cholesterol and lipid phosphorus values for partially nephrectomized and control rats fed diets containing varying concentrations of dried extracted liver

METHODS

The operative procedure for unilateral and partial nephrectomy, the methods for estimating blood pressure and renal function and the care of the experimental animals have been described⁴ When the animals were 60 to 70 days of age they were placed on one of the experimental diets the composition and cholesterol content of which are listed in table 1 The five diets were designated EL 10,

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This investigation was made possible by the Edward N Gibbs Prize Fund of the New York Academy of Medicine

1 Cantarow, A Cholesterol Metabolism, *Internat Clin* **1** 237, 1935

2 Page, I H, Kirk, E, and Van Slyke, D D Plasma Lipids in Chronic Hemorrhagic Nephritis, *J Clin Investigation* **15** 101, 1936

3 Sinclair, R The Physiology of the Phospholipids, *Physiol Rev* **14** 351, 1934

4 Chanutin, A, and Ludwig, S Experimental Renal Insufficiency Produced by Partial Nephrectomy V Diets Containing Whole Dried Meat, *Arch Int Med* **58** 60 (July) 1936

EL 20, EL 40, EL 60 and EL 80, in accordance with the percentage of dried extracted liver, which was the principal source of protein. The dried extracted liver was prepared from cold storage hog liver which was thoroughly extracted with hot water and dried.

The minimum period of the experimental diet was sixty days, but in most instances the diet was continued from ninety to one hundred and fifty days before the animal was killed. Blood was drawn from the abdominal aorta while the animal was under ether anesthesia, and heparin was used as the anticoagulant. The method of Schoenheimer and Sperry,⁵ with slight modifications,⁶ was used for determining the free and total cholesterol values. Phospholipid phosphorus values were determined according to the procedure recommended by Man and Peters.⁷ Statistical analyses were done according to standard methods.⁸

RESULTS

Plasma Cholesterol Values for Control Animals (One or Two Kidneys) and Partially Nephrectomized Rats—The individual values for total cholesterol and the percentage of esterified cholesterol in the

TABLE 1—Composition of Rations

Diet	Dried Ex- tracted Liver	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Cholesterol, %		
							Total	Free	Esters
EL 10	10	62	14	5	5	4	0.16	0.13	23
EL 20	20	52	14	5	5	4	0.29	0.19	34
EL 40	40	32	14	5	5	4	0.55	0.37	32
EL 60	60	12	14	5	5	4	0.72	0.45	37
EL 80	80	6		4	6	4	1.07	0.63	42

plasma of control and partially nephrectomized rats fed diets containing 10, 20, 40, 60 or 80 per cent dried extracted liver are presented in figure 1. The mean values for the total cholesterol for the control animals were about the same with the exception of the elevated value with diet EL 80. These average values, in milligrams per hundred cubic centimeters, with standard errors, were 86 ± 2.32 , 86 ± 2.89 , 90 ± 3.72 , 92 ± 4.02 and 122 ± 4.01 , respectively. On the other hand, the mean values for plasma total cholesterol for the partially nephrectomized rats showed an irregular increase with the increased percentage of cholesterol in the respective extracted liver diet. These average

5 Schoenheimer, R., and Sperry, W. M. A Micromethod for the Determination of Free and Combined Cholesterol, *J Biol Chem* **106** 745, 1934.

6 Chanutin, A., and Ludewig, S. The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, *J Biol Chem* **115** 1, 1936.

7 Man, E. B., and Peters, J. P. Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method, with a Note on the Estimation of Lipoid Phosphorus, *J Biol Chem* **101** 685, 1933.

8 Garrett, H. E. Statistics in Psychology and Education, New York, Longmans, Green & Co., 1930.

values, in milligrams per hundred cubic centimeters, with standard errors, were 111 ± 2.98 , 129 ± 2.89 , 125 ± 3.68 , 144 ± 4.09 and 150 ± 5.56 , respectively. These values were higher than those for the control animals in the respective dietary groups. A statistical analysis of the reliability of the difference between the means for the control and those for the partially nephrectomized animals with the same diet showed a significant difference in all cases. For all dietary groups the percentage of esterified cholesterol remained fairly constant, despite the wide variations in the total cholesterol concentrations. Hypoproteinemia was never encountered in these animals.

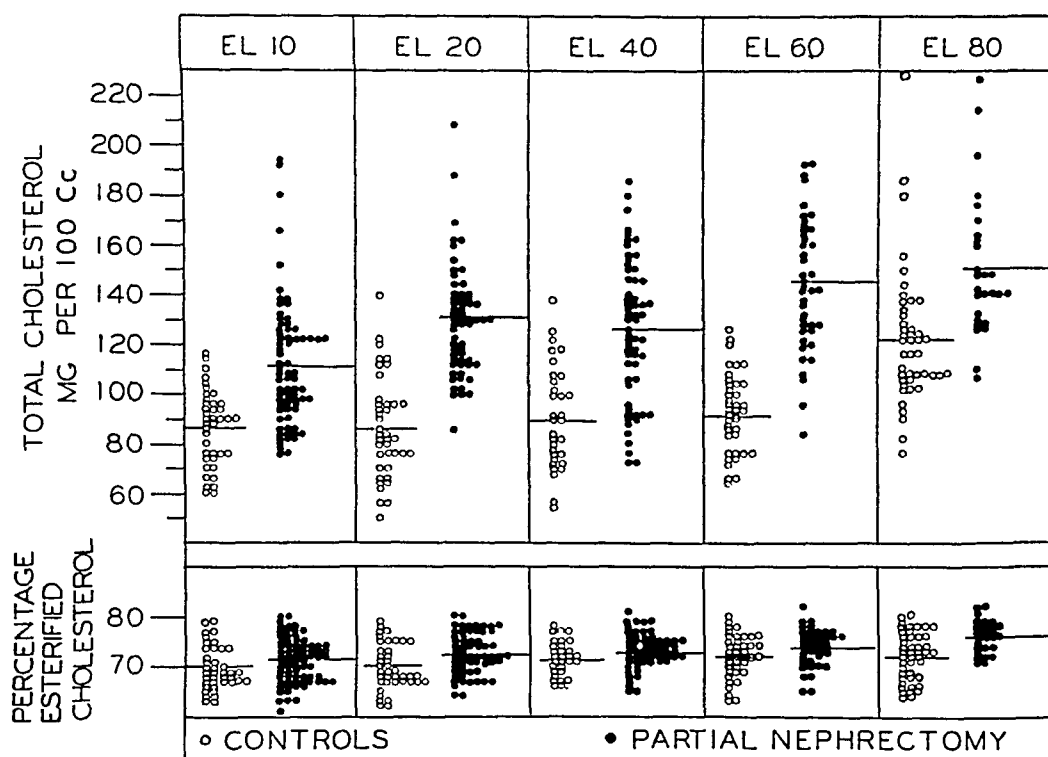


Fig 1—Cholesterol values for control and partially nephrectomized rats fed various diets containing dried extracted liver

It is obvious that renal insufficiency produced by partial nephrectomy affects cholesterol metabolism, as evidenced by the plasma cholesterol concentration. It has been shown⁹ that the plasma cholesterol was greater for partially nephrectomized rats than for controls fed a diet supplemented with 2.5 per cent cholesterol. Best, Grant and Ridout¹⁰ have shown that increasing amounts of protein (casein, dried egg white and beef muscle) in the diet prevented the accumulation of fat in the

9 Chanutin, A, and Ludewig, S. The Effect of Cholesterol Ingestion on Tissue Lipids of Rats, *J Biol Chem* **102** 57, 1933

10 Best, C H, Grant, R, and Ridout, J H. The "Lipotropic" Effect of Dietary Protein, *J Physiol* **86** 337, 1936

liver of the white rat. This lipotropic effect was difficult to gage in the present experiments because there was a progressive increase in both the protein and the cholesterol content of the diets. It is probable that the slight increase in plasma cholesterol encountered for control animals fed diets containing about 1 per cent cholesterol (diet EL 80) may have been due to the excessive amount of cholesterol in relation to the protein content.

Despite the presence of appreciable amounts of cholesterol in the diets fed in these experiments, gross examination of the livers revealed no fatty changes. Blatherwick and his associates¹¹ demonstrated that diets rich in whole dried liver caused the development of a fatty liver in the rat. On the other hand, similar quantities of dried, water-extracted liver did not produce these fatty changes. This finding has been confirmed in this investigation.

TABLE 2—*Ratio of Free Cholesterol to Phospholipid Phosphorus for Control and Partially Nephrectomized Rats**

Diet	Control Rats	Partially Nephrectomized Rats
EL 10	3.5 (35)	3.6 (71)
EL 20	3.7 (19)	3.9 (44)
EL 40	3.7 (15)	3.6 (59)
EL 60	3.7 (15)	3.8 (39)
EL 80	3.7 (36)	3.8 (27)

* The figures in parentheses indicate the number of rats.

Relation of Free Cholesterol and Phospholipid Values—The average $\frac{\text{free cholesterol}}{\text{phospholipid phosphorus}}$ ratios for the control and partially nephrectomized rats are presented in table 2. It is seen that the ratios are constant for both groups of animals. The phospholipid phosphorus concentration varied from 4.3 to 15.3 mg per hundred cubic centimeters. A similar direct relation was demonstrated in rats subjected to partial hepatectomy and to ligation of the bile duct⁶ and in man with hepatic damage.¹²

Relation Between Total Cholesterol Value, Urea Ratio and Blood Pressure—The relation between the total cholesterol value and the urea ratio, $\frac{\text{urine excreted per hour}}{\text{urea in 100 cc of blood}}$, is presented in figure 2. It can be seen that the concentration of plasma cholesterol was not closely related to the degree of renal insufficiency. In figure 3 the total cholesterol value

¹¹ Blatherwick, N. R., Medlar, E. M., Bradshaw, P. J., Post, A. L., and Sawyer, S. D. The Dietary Production of Fatty Livers in Rats, *J. Biol. Chem.* **103** 93, 1933.

¹² Chanutin, A., and Ludewig, S. Blood Lipid Studies in a Case of Xanthomatosis Associated with Hepatic Damage, *J. Lab. & Clin. Med.* **22** 903, 1937.

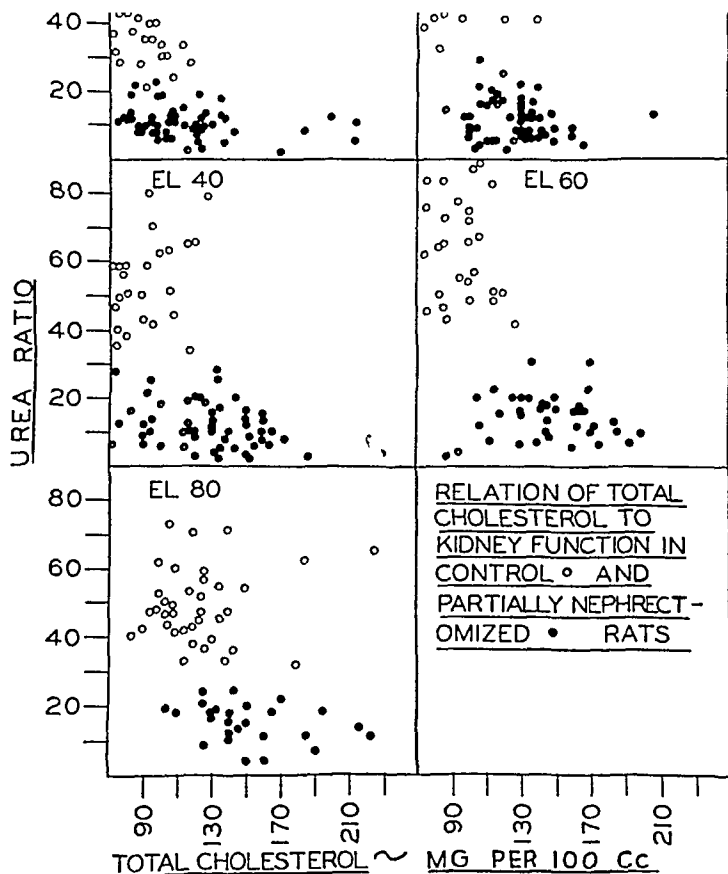


Fig 2—Relation of total cholesterol value to renal function of control and partially nephrectomized rats

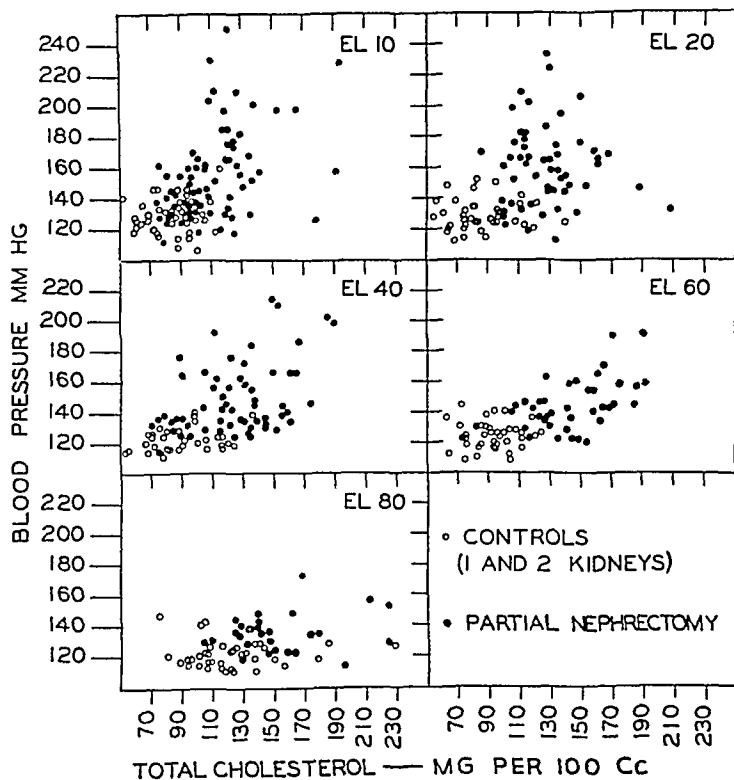


Fig 3—Comparison of the total cholesterol values and the blood pressure

is compared with the blood pressure. There was no definite relation between the height of the blood pressure and the plasma cholesterol concentration.

SUMMARY AND CONCLUSIONS

The plasma cholesterol and phospholipid phosphorus concentrations have been determined for control (one or two kidneys) and partially nephrectomized rats fed diets containing varying percentages of dried extracted liver (10, 20, 40, 60 and 80 per cent) and cholesterol (0.16 to 1.07 per cent).

There was no increase in the mean concentration of the plasma cholesterol for control animals except for those receiving diet EL 80. There was an increase in the cholesterol values for the partially nephrectomized rats which appeared to be roughly associated with the amount of ingested cholesterol. There was no relation between the total plasma cholesterol concentration and the renal function or the blood pressure. The phospholipid phosphorus value varied directly with the free cholesterol concentration for both the control and the partially nephrectomized animals. The percentage of cholesterol esters was unchanged by operation or by diet.

Since renal insufficiency produced by partial nephrectomy appears to affect the ability of the rat to metabolize cholesterol, it is likely that cholesterol disturbances in renal diseases of man are directly associated with renal damage.

SIZE AND SHAPE OF THE HEART IN HYPERTHYROIDISM

A TELEROENTGENOGRAPHIC STUDY OF TWO HUNDRED CASES

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Until recently "thyroid heart" was considered to be a definite entity and was admitted without discussion as a member of the group of organic cardiac diseases. This idea is now losing popularity, and the tendency to consider so-called thyroid heart as a simple functional disorder is becoming more and more prevalent.

The fundamental reasons for this change are based on experimental proof—pathologico-anatomic, electrocardiographic and roentgenographic, though none of these has been capable of showing definitely the existence of a constant specific alteration in the heart in hyperthyroidism. Thus, Takane¹ and Boyksen² have found infiltration or degenerative changes in the hearts of rats intoxicated with thyroid preparations, whereas Goodpasture³ found only slight alterations in rabbits under similar conditions, but he admitted that there might exist an increased liability of the myocardium to infection. Rake and McEachern⁴ said they considered that the lesions they observed were of no importance. Simonds and Brandes,⁵ working with dogs, mentioned only hypertrophy.

Postmortem examination of the human subject also has given rise to divergent interpretations. Fahr and Kuhle⁶ observed hypertrophy,

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1 Takane, K. Pathobiogenese der Myocarditis acuta durch organische und anorganische Jodbindungen bzw. der Basedowmyokarditis, *Virchows Arch f path Anat* **259** 1, 1926, Ueber die experimentelle akute Myokarditis durch Thyreoidin und Jodsalze, *ibid* **259** 737, 1926.

2 Boyksen, D. Thyreotoxische Herzmuskelschädigungen, *Virchows Arch f path Anat* **293** 342, 1934.

3 Goodpasture, E. The Influence of Thyroid Products on the Production of Myocardial Necrosis, *J Exper Med* **34** 407, 1921.

4 Rake, G., and McEachern, D. Experimental Hyperthyroidism and Its Effects upon the Myocardium in Guinea Pigs and Rabbits, *J Exper Med* **54** 23, 1934.

5 Simonds, J. P., and Brandes, W. W. The Size of the Heart in Experimental Hyperthyroidism, *Arch Int Med* **45** 503 (April) 1930.

6 Fahr, T., and Kuhle, J. Zur Frage des Kropfherzens und der Herzveränderungen bei Status thymolymphaticus, *Virchows Arch f path Anat* **233** 286, 1921.

myodegeneration, callus formation and lymphocytic infiltration and said they concluded that myocarditis could be attributed to the thyroid disease, although they recognized the nonspecific character of the lesion. Boyksen² made similar observations and also described necrotic alterations. Baust⁷ mentioned only a slight increase of lymphocytes, histiocytes and fibroblasts. De Chatel and Molnár⁸ observed dark brown pigmentation, an increase of connective tissue and slight hypertrophy. On the other hand, Cabot,⁹ Rake and McEachern,¹⁰ Lewis,¹¹ Weller, Wanstrom, Gordon and Bugher,¹² and Friedberg and Sohval¹³ did not note much change, and when they did they attributed it to concomitant lesions due to rheumatism, arteriosclerosis, syphilis or some other disease. References to publications based on the observations made at only a small number of autopsies have been omitted.

In electrocardiographic studies there is agreement in the frequency with which auricular fibrillation occurs, but there the unanimity ends. Hoffmann,¹⁴ Strubell,¹⁵ Krumbhaar,¹⁶ Haas and Parade,¹⁷ Gossels,¹⁸ and McGuire and Foulger¹⁹ have said they consider that a high T wave is characteristic of hyperthyroidism, but Smith and Colvin,²⁰

7 Baust, H. Ueber histologische Befunde an Kropfherzen, Beitr z path Anat u z allg Path **86** 543, 1931

8 de Chatel, A., and Molnar, W. Herzveränderungen bei Morbus Basedow, Virchows Arch f path Anat **289** 557, 1933

9 Cabot, R. Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 723

10 Rake, G., and McEachern, D. A Study of the Heart in Hyperthyroidism, Am Heart J **8** 19, 1932

11 Lewis, W. Hyperthyroidism and Associated Pathology, Am J M Sc **171** 65, 1931

12 Weller, C. V., Wanstrom, R. C., Gordon, H., and Bugher, J. C. Cardiac Histopathology in Thyroid Disease, Am Heart J **8** 8, 1932

13 Friedberg, C., and Sohval, A. The Occurrence and the Pathogenesis of Cardiac Hypertrophy in Graves' Disease, Am Heart J **13** 599, 1937

14 Hoffmann, A. Die Elektrographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Munich, J. F. Bergmann, 1914, p. 115

15 Strubell, A. Ueber die Klinik des Elektrokardiogramms, Deutsche med Wchnschr **38** 988, 1912

16 Krumbhaar, E. Electrocardiographic Observations in Toxic Goiter, Am J M Sc **155** 175, 1928

17 Haas, M., and Parade, G. Untersuchungen bei Morbus Basedow vor und nach Schilddrüsenresektion, Beitr z klin Chir **152** 111, 1931

18 Gossels, C. Klinischer Beitrag zur Frage des Elektrokardiogramms bei Schilddrüsenveränderungen, Deutsches Arch f klin Med **173** 597, 1932

19 McGuire, J., and Foulger, M. The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram with Special Reference to the T-Waves, Am Heart J **8** 114, 1932

20 Smith, F., and Colvin, L. Certain Cardio-Vascular Features of Hyperthyroidism, Ann Clin Med **5** 616, 1927

Franke,²¹ White,²² Misske and Schone²³ and Gotta²⁴ have not expressed agreement with this

Roentgenographic studies have revealed the so-called thyroid heart in two of its aspects—shape and size Otten,²⁵ Kerr and Hensel,²⁶ Rosler,²⁷ Meyer-Borstel,²⁸ Parkinson and Cookson,²⁹ Cookson³⁰ and Peserico³¹ have admitted that hyperthyroidism causes a bulging of the left middle arch, which makes the cardiac shadow show the so-called mitral configuration, according to some authors,³² when the hyperthyroidism is prolonged, the cardiac area is enlarged chiefly on the left side On the other hand, Hawley³³ has maintained that the so-called thyroid heart has no characteristic shape, and Misske and Schone³⁴ have attributed the mitral configuration in cases of hyperthyroidism to purely constitutional factors Hamilton,³⁵ Smith and Colvin,²⁰ Deneen³⁶ and Hurxthal and Menard³⁷ have stated that the heart in hyperthyroidism is of normal size or only slightly enlarged and that in

21 Franke, W Das Elektrokardiogram bei Schilddrüsenerkrankungen, *Deutsches Arch f klin Med* **159** 180, 1928

22 White, P D Heart Disease, New York, The Macmillan Company, 1935, p 379

23 Misske, B, and Schone, G Das Elektrokardiogramm bei Schilddrüsenüberfunktion, *Ztschr f klin Med* **125** 387, 1933

24 Gotta, H Contribucion al estudio de la tirotoxicosis, Buenos Aires, Frascoli y Bindi, 1931, p 44

25 Otten, M Die Bedeutung der Orthodiagraphie für die Erkennung der beginnenden Herzerweiterung, *Deutsches Arch f klin Med* **105** 370, 1910

26 Kerr, W J, and Hensel, G C Observations of the Cardiovascular System in Thyroid Disease, *California State J Med* **20** 306, 1922, *Arch Int Med* **31** 398 (March) 1923

27 Rosler, H Das Röntgenbild des Herzens beim hyperthyroidismus, *Wien Arch f inn Med* **15** 539, 1928

28 Meyer-Borstel, H Ueber Form- und Grossenveränderungen des Herzens bei Struma, *Fortschr a d Geb d Röntgenstrahlen* **41** 695, 1930

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30 Cookson, H The Size and Shape of the Heart in Goiter, *Proc Roy Soc Med* **25** 1517, 1932

31 Peserico, E Le cardiopatie nell'ipertiroidismo, cuore e circolaz **18** 83, 1934

32 Kerr and Hensel²⁶ Parkinson and Cookson²⁹ Cookson³⁰

33 Hawley, S A Roentgen Study of the Chest in Two Hundred Patients with Goiter, *Am J Roentgenol* **32** 326, 1934

34 Misske, B, and Schone, G Das Herz im Röntgenbilde bei Schilddrüsenüberfunktion, *Fortschr a d Geb d Röntgenstrahlen* **50** 121, 1935

35 Hamilton, B Heart Failure of the Congestive Type Caused by Hyperthyroidism, *J A M A* **83** 405 (Aug 9) 1924

36 Deneen, F The Heart in Goiter Conditions, *Illinois M J* **55** 264, 1929

37 Hurxthal, L, and Menard, O The Size of the Heart in Goiter A Tele-radiographic Study, *Am J M Sc* **180** 772, 1930

the cases in which there is enlargement of the cardiac area there is other cardiovascular disease present, notably rheumatism, hypertension arteriosclerosis or syphilis

This contradictory state of opinion has led to the publication of this work, based on the clinical, electrocardiographic and teleroentgenographic study of a series of 200 cases of hyperthyroidism. The teleroentgenographic study was repeated after various intervals in 86 cases, in 12 cases the hyperthyroidism persisted, and in 74 cases recovery had been achieved.

The clinical examination was performed by me in every case, and the diagnosis was confirmed by means of repeated basal metabolic estimations. The teleroentgenograms were made with the patient upright, with frontal projection at a focal distance of 2 meters, with an exposure of one-tenth second and during normal inspiration.

The internal diameter of the chest and the transverse and long diameters of the heart were measured on each roentgenogram, and the changes in shape and size were noted. The size of the cardiac area was classified as normal, slightly enlarged, appreciably enlarged or greatly enlarged. The classification was made according to personal judgment, which is naturally open to criticism, but in spite of the imperfections of such a method, it seemed preferable to the use of the cardi thoracic index or tables of standard values, which do not take into account individual constitutional variations. On the other hand, the expressions normal, appreciably enlarged and greatly enlarged correspond to a definite concept that is easy to interpret. This is not so, however, when the term slightly enlarged is used. In this category were placed the cases in which enlargement was doubtful, and it included a borderline or transitional appearance between normal and undoubted enlargement.

With this classification it was found that the cardiac area was normal in 80 cases of hyperthyroidism, slightly enlarged in 64, appreciably enlarged in 30 and greatly enlarged in 26.

Next it was decided to investigate whether this discrepant variation was due to the influence of any of the following factors: (1) the age of the patient, (2) the duration of hyperthyroidism, (3) the intensity of hyperthyroidism or (4) associated cardiovascular disease.

1. In order to investigate a possible relation between the size of the cardiac area and the age of the patient, the patients were divided into three groups according to age: in the first those under 29, in the second, those from 30 to 49, and in the third, those over 50.

Table 1 shows the results of this classification. In each column under the number of patients is given the percentage in relation to the total of patients in the group. The total number of patients in each group, was as follows: 93 in the first, 83 in the second and 24 in the third.

Comparing the percentages it can be seen that of those under 29 years half showed a normal cardiac area, one-third showed slight enlargement and a small number showed great enlargement. For those

between 30 and 49 years of age, these differences lessened and for those over 50 the proportions changed, only one-sixth showing a normal cardiac area and more than one-third showing great enlargement. Thus, with these statistical data it can be asserted that the number of patients with hyperthyroidism who show enlargement of the cardiac area increases with age.

2 In order to investigate the possibility of a relation between the size of the heart and the duration of hyperthyroidism, the patients were divided into three groups according to whether the disease had existed (1) for less than one year, (2) for from one to five years or (3) for more than five years.

TABLE 1—*Relation of Age to the Cardiac Area*

Age Group	Number of Patients	Cardiac Area			
		N	+	++	+++
Less than 29 years	93	44 47%	32 34%	13 14%	4 4%
Between 30 and 49 years	83	32 38%	26 31%	12 14%	13 15%
Over 50	24	4 16%	6 25%	5 20%	9 37%

* In tables 1 to 6, N indicates normal +, slight enlargement, ++, appreciable enlargement, +++, great enlargement.

TABLE 2—*Relation of the Duration of Hyperthyroidism to the Cardiac Area*

Duration of Hyperthyroidism	Number of Patients	Cardiac Area			
		N	+	++	+++
Less than 1 year	70	33 47%	22 31%	11 15%	4 6%
1 to 5 years	82	32 39%	27 32%	7 8%	16 19%
More than 5 years	42	14 33%	14 33%	9 21%	5 11%

Table 2 shows the result of this classification. Each column gives the number of cases and the corresponding percentage in relation to the total number of patients. The total numbers were 70, 82 and 42, respectively, for the three groups, 6 patients were not included, as the time of beginning of the disease in these cases could not be established.

Comparison of the percentages revealed that as the disease continued, the relative number of patients with a normal cardiac area diminished and the number of patients with cardiac enlargement increased, but this increase was not regular nor very significant, as can be seen by comparing the figures in the last two columns.

Considering the table as a whole, one may assume that there is a relation, though indeed not pronounced, between the cardiac area and the duration of the hyperthyroidism.

3 To examine the possibility of a relation between the cardiac area and the degree of hyperthyroidism, the patients were divided into the three following groups according to the basal metabolic rate under + 35 per cent, between + 35 per cent and + 50 per cent and above + 50 per cent

In accordance with the system adopted for the preceding tables, in table 3 each column contains the number of patients and the corresponding percentage in relation to the total number of patients in the group. The totals were 38, 67 and 95, respectively, for the three groups.

Examination of the percentages shows that among patients with moderate hyperthyroidism, the proportion of normal cardiac areas was relatively greater than for those with more intense hyperthyroidism. These statistical data suggest the existence of a relation between the intensity of hyperthyroidism and the cardiac area, but it is not sufficiently decisive to be stated definitely.

TABLE 3—*Relation of the Basal Metabolic Rate and the Cardiac Area*

Basal Metabolic Rate	Number of Patients	Cardiac Area			
		N	+	++	+++
Under +35%	38	21 55%	13 34%	2 5%	2 5%
+35 to +50%	67	33 49%	18 26%	10 14%	6 9%
Above +50%	95	26 27%	33 34%	18 18%	18 18%

4 The existence of diseases recognized as capable of producing enlargement of the cardiac area, particularly arteriosclerotic disease, hypertension, rheumatism and renal disease with hypertension, was carefully investigated in each case of hyperthyroidism both from the clinical and from the roentgenographic point of view. The diagnosis was carefully made and was based on undoubted symptoms. Some patients had symptoms which indicated that cardiovascular lesions might be presumed to be present, but this point could not be definitely affirmed or denied, in these instances the symptoms were considered as non-existent.

A diagnosis of arterial hypertension was made only for those patients in whom this condition persisted after they had recovered from hyperthyroidism, thus covering the objections of those who maintain that hyperthyroidism per se can cause hypertension (Parkinson and Hoyle³⁸), in only 2 cases of hyperthyroidism, in which the patients have been followed for eight and seven years, respectively, and in which cure has

38 Parkinson, J, and Hoyle, C. Thyrotoxic Hypertension, *Lancet* 2 913, 1934

not yet been obtained, was this condition not fulfilled, but the high blood pressure in these cases makes the diagnosis certain

A diagnosis of rheumatism was made only for those patients who had an absolutely characteristic history of rheumatic fever or chorea or of aortic regurgitation not due to other known causes or when the existence of mitral stenosis was confirmed after recovery from hyperthyroidism. In this way mistakes due to the frequency and variety of murmurs which occur during hyperthyroidism were avoided. The case of a woman who had a greatly enlarged heart was also included, although the rheumatic origin could not be proved, this patient was not followed afterward, but she died later from an attack of tetany, and pericardial effusion was present at autopsy.

Sclerotic disease of the aorta was noted in 23 cases, arterial hypertension in 14, a history of or actual rheumatic lesions in 19 and glomerular nephritis in 4.

TABLE 4—*Relation of Associated Diseases to Cardiac Area*

Associated Disease	Number of Patients	Cardiac Area			
		N	+	++	+++
Sclerotic aortic disease	23	3	5	8	7
Hypertension	14		5	2	7
Rheumatism	19	2	3	9	5
Glomerular nephritis	4		1	1	2
Totals	60	5	14	20	21

In table 4 the patients suffering from these diseases are grouped according to the size of the heart.

Comparing the total number of patients in the corresponding groups in which some other disease was present as well as hyperthyroidism, it is seen that 21 (80 per cent) of the 26 patients with great enlargement of the heart had some associated disease which was admittedly capable of producing cardiac enlargement. Twenty (66 per cent) of the 30 patients who had an appreciable enlargement of the heart had also one of the four previously mentioned diseases. The percentages were reduced to 21 and 6 per cent, respectively, for those with a moderately enlarged or normal heart.

It can therefore be concluded that the greater number of patients with hyperthyroidism and enlargement of the heart have some other disease which would account for this enlargement.

5 Twelve patients were studied roentgenographically on two separate occasions during the disease, the second roentgenogram being taken when the hyperthyroidism was still present or even—and this must be emphasized—of greater intensity than at the previous examination. In table 5 each case is individually analyzed.

TABLE 5.—Summary of Data Obtained from Two Teleoentgenographic Studies During Hypothyroidism

Patient No	Age, Yr	Duration of disease, Yr	Teleoentgenograms										Interval Between Two Roentgenograms, Yr	Comment
			First					Second						
			Cardiac Diameters, Cm			Cardiac Area	Internal Diam of Chest, Cm	Cardiac Diameters, Cm			Cardiac Area	Internal Diam of Chest, Cm		
			Long	Transverse	Long			Transverse	Long	Transverse				
1	35	14	155	137	30.0	N	32.1	145	134	32.1	N	7	Diaphragm was lower in second plate, thus accounting for apparently reduced area	
2	27	14	150	114	25.3	N	24.2	130	120	24.2	N	2	Diaphragm was raised in second plate, thus accounting for apparently increased area	
3	42	1	134	111	26.5	N	24.0	154	116	24.0	N	1	Progressive rheumatic heart disease	
4	6	1	81	75	17.0	N	20.3	131	115	20.3	† † †	1	Arterial hypertension	
5	44	1	150	142	24.5	†	26.0	150	140	26.0	†	1	Sclerotic aortic disease	
6	52	17	152	143	25.0	†	27.4	154	140	27.4	†	1	Sclerotic aortic disease	
7	56	22	146	128	28.0	† †	27.2	142	130	27.2	† †	3	Rheumatic endocarditis	
8	59	1	143	131	24.0	† †	24.0	140	133	24.0	† †	6	Arterial hypertension, maximum 15 mm., minimum 7 mm. in 1929, maximum 19 mm., minimum 9 mm. in 1935	
9	25	15	134	132	23.5	† †	24.5	146	141	24.5	† †	5	Arterial hypertension, maximum 14 mm., minimum 8 mm. in 1930, maximum 19 mm., minimum 11 mm. in 1937	
10	38	10	143	140	23.0	† †	24.2	138	138	24.2	† †	6	Amyocardial fibrillation, congestive heart failure	
11	38	1	150	147	24.0	† †	?	160	142	?	† †	2	Glomerulonephritis	
12	24	1	148	138	25.6	† †	27.5	177	173	27.5	† † † †	1		

In 7 cases (1 to 3 and 5 to 8) there was no increase in the cardiac area during the two years and three months, which was the average time which elapsed between the taking of the two roentgenograms. Case 1 is worthy of special mention since the second roentgenogram was not taken until seven years after the first, when the hyperthyroidism was clearly worse.

In 3 cases there was a moderate increase in the size of the heart. In cases 9 and 10 this coincided with the increase in arterial hypertension which was associated with the hyperthyroidism, while in case 11 the enlargement was not significant, as the patient also suffered from auricular fibrillation and congestive heart failure.

There remain for consideration cases 4 and 12, in which there was considerable increase in the size of the heart after a relatively short interval, in the first case this was due to rheumatic carditis and in the second to rapidly progressive glomerular nephritis.

Thus, in none of these cases did hyperthyroidism by itself seem capable of producing cardiac enlargement. In every case in which cardiac enlargement did occur, it could be satisfactorily explained as due to some other disease that was present at the same time.

6 Seventy-four patients were studied roentgenographically a second time after they had been submitted to subtotal thyroidectomy, 27 showed a normal cardiac area, 31, slight enlargement, 7, appreciable enlargement, and 9, great enlargement. The clinical examination and basal metabolic results showed that the hyperthyroidism had been cured. The interval between operation and the taking of the roentgenogram varied greatly, owing to individual circumstances, in some cases, when the patient had to return to the province, the interval was scarcely a month, but usually it was more than a year, and in some cases it even reached six or seven years.

On comparison of these roentgenograms and those obtained while the patients were under the influence of hyperthyroidism, three types of conditions were noted. The cardiac area was larger, equal or smaller. The cardiac area was considered as not having changed when the difference in measurements of the long and of the transverse diameter of the heart in the two roentgenograms was less than 0.5 cm. It is extremely difficult to take two roentgenograms under exactly similar conditions, since the heart may not be in the same period of contraction and the patient may hold his breath at a different movement of respiration, hence, a slight difference in measurement must be overlooked.

By using this criterion it was found that after recovery from hyperthyroidism there was no change in the cardiac area in 38 cases, 1 e.,

more than half the cases (18 patients had a normal cardiac area 15 slight enlargement, 4, appreciable enlargement, and 1, great enlargement)

The cardiac area was larger in the second roentgenogram in 23 cases (8 patients showed a normal area, 10, slight enlargement, 2, appreciable enlargement, and 3, great enlargement) In some cases there may have been only apparent enlargement, owing to the causes previously mentioned, but in others it might have been a true enlargement, resulting from the cessation of tachycardia, from the progress of preexisting lesions unrelated to hyperthyroidism or from some new disease Whatever the reason may have been, no useful knowledge is added to the problem of the so-called thyroid heart because, obviously, this enlargement of the cardiac area cannot be a result of the recovery from hyperthyroidism

The cardiac area was smaller in the second roentgenogram in 13 cases In 3 cases the decrease was probably only apparent, since the diaphragm was lower than in the original roentgenogram and it is known that when inspiration is deeper the frontal projection of the heart is reduced

Excluding these, there remain 10 patients (4 with slight enlargement of the cardiac area, 1 with appreciable enlargement and 5 with great enlargement) who almost certainly showed a real decrease in the cardiac volume, although the cardiac area remained larger in comparison with the normal heart Of these patients, 1 had coronary disease, 1 had arteriosclerotic aortic disease and congestive heart failure, 1 had active rheumatism, 1 had a history of rheumatic fever and congestive heart failure, 4 had permanent auricular fibrillation (3 of these also had arterial hypertension and the fourth patient had congestive heart failure) In the 4 with auricular fibrillation the sinus cardiac rhythm had been established when the second roentgenogram was taken, and all with congestive heart failure had recovered or improved

It appears, therefore, that the patients in whom the heart became smaller on recovery from hyperthyroidism almost always showed some associated cardiovascular disease, which also explains why, in spite of this decrease in size, the heart remained larger than normal, as has already been stated

Thus, in more than half the patients studied, recovery from hyperthyroidism was not accompanied with modification of the cardiac area, in about one third of the patients for whom an increase in the cardiac area was found, this could not logically be attributed to the hyperthyroidism, the decrease in the cardiac area found in less than one seventh of the patients almost always occurred in cases of hyperthyroidism associated with cardiovascular disease Meyer-Borstel²³

Menard and Hurxthal,³⁹ Rosenblum and Levine⁴⁰ and Parade and Rahm,⁴¹ who have also made comparative studies of the cardiac area before and after recovery from hyperthyroidism, arrived at a similar conclusion

COMMENT

An attempt will now be made to rationalize the conclusions which were reached

According to the tables, it has been seen that there exists a relation between the cardiac area and certain other factors, none of which have such a distinct influence as the coexistence of cardiovascular disease. This is so evident that it suggests the possibility that the undoubted influence of age and, in a lesser degree, the influence due to the duration and intensity of the hyperthyroidism have an effect only when heart disease is also present. In order to justify this assertion the previously mentioned factors will be reconsidered in the same order.

Age—The number of patients over 30 years of age with an appreciably or greatly enlarged heart was 39, of these, 31 had associated cardiovascular disease. These figures need no comment, and it can be affirmed that although the proportion of hyperthyroidism in patients with enlargement of the heart increases with age, the latter is not the determining factor. This finding is merely due to the fact that the percentage of persons with cardiovascular disease also increases with age.

Duration of Hyperthyroidism—The statistical data concerning the influence of the duration of hyperthyroidism on the heart were not conclusive. There was a slight relation between these two factors, but it is necessary to examine this point further.

It will be remembered that for 7 patients who were studied roentgenographically twice, with an average of two and one-fourth years' time between the two examinations, there was no difference in the cardiac area.

The number of patients suffering from hyperthyroidism of more than one year's standing who showed an appreciably or greatly enlarged cardiac area was 37 (table 2), and 27 of these had associated cardiovascular disease.

These observations enable one to deduce that the duration of hyperthyroidism itself is not the responsible factor in the enlarging of the

³⁹ Menard, O., and Hurxthal, L. Changes Observed in the Heart Shadow in Toxic Goiter Before and After Treatment, *Ann Int Med* **6** 1634, 1933.

⁴⁰ Rosenblum, H., and Levine, S. What Happens Eventually to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? *Am J M Sc* **185** 219, 1933.

⁴¹ Parade, G. W., and Rahm, H. Ueber das Verhalten der Herzgrosse bei Morbus Basedow nach Schilddrüsenresektion, *Ztschr f klin Med* **126** 667, 1934.

cardiac area Hurxthal and Menard,³⁷ Read⁴² and Lerman and Means⁴³ have stated that they agree with this, but it is not in accordance with the postmortem observations of Kepler and Barnes,⁴⁴ who found that there was a relation between the increase in weight of the heart, i e, hypertrophy, and the duration of hyperthyroidism

Intensity of Hyperthyroidism—The statistical data, as such, do not permit the assertion that the intensity of hyperthyroidism is a definite factor in the increase in the cardiac area, but these figures become more significant when it is realized that 28 of the 36 patients with a basal metabolic rate above + 50 per cent and an appreciably or greatly enlarged cardiac area (table 3) had associated cardiovascular disease

It can therefore be affirmed that the intensity of hyperthyroidism is not a factor which causes variations in the size of the heart Kepler and Barnes,⁴⁴ in mentioning the results of many autopsies, said that they had observed no relation between the weight of the heart and the intensity of the hyperthyroidism

A further confirmation of this assertion is found in the group of patients with thyrocardiac disease (Lahey) who frequently show only a moderate increase in the basal metabolic rate but marked cardiopathic symptoms, particularly enlargement of the heart

Besides, during a crisis of hyperthyroidism, i e, in maximum hyperthyroidism, cardiac failure, according to Willus and Boothby,⁴⁵ Hamilton⁴⁶ and Andrus,⁴⁷ does not usually occur, as I also have seen in such cases Moreover, autopsies on patients with hyperthyroidism who die during the crisis do not reveal enlargement of the heart (Cabot⁹)

The decrease in cardiac area after recovery from hyperthyroidism observed in some cases can be explained in the following way Hyperthyroidism imposes extra work, which must be performed by a heart already weakened by cardiovascular disease, which was present in almost all the patients examined, when hyperthyroidism was cured, the conditions under which the heart worked were improved, and the size of the heart therefore decreased

42 Read, M Cardiac Status After Prolonged Thyrotoxicosis, *Am Heart J.* 8 84, 1932

43 Lerman, J, and Means, J Cardiovascular Symptomatology in Exophthalmic Goiter, *Am Heart J* 8 55, 1932

44 Kepler, E, and Barnes, A Congestive Heart Failure and Hypertrophy in Hyperthyroidism, *Am Heart J* 8 102, 1932

45 Willus, F, and Boothby, W The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, *M Clin North America* 7 189, 1923

46 Hamilton, B Clinical Notes on Hearts in Hyperthyroidism, Boston *M & S J* 186 216, 1922

47 Andrus, E The Heart in Hyperthyroidism A Clinical and Experimental Study, *Am Heart J* 8:66, 1932

It can be concluded that age and the duration and intensity of the hyperthyroidism are not determining factors in the enlargement of the cardiac area which is found in some patients with hyperthyroidism

Mitral Configuration—It has been said by certain authors⁴⁸ that the cardiac shadow in cases of hyperthyroidism often shows mitral configuration. The frequency of the bulging of the left middle arch was examined, only 4 of the 67 patients in whom it was found had mitral stenosis. The age of the patient, the intensity and duration of hyperthyroidism and the size of the heart had no influence on the production of this shape (statistical data are suppressed), hence, it can be looked on as of constitutional origin (Borak,⁴⁹ Nemet⁵⁰ and Misske and Schone³⁴) and not as mitral configuration due to hyperthyroidism. This interpretation is also supported by the fact that in 26 patients with so-called mitral configuration, the latter persisted when roentgenograms were made after recovery from the hyperthyroidism, there being a decrease in the curvature of the left arch in only a few cases.

TABLE 6—*Relation of Electrocardiographic Findings to Cardiac Area*

Electrocardiographic Findings	Number of Patients	Cardiac Area			
		N	+	++	+++
Normal	108	55	37	11	5
Auricular fibrillation	13	1	2	5	5
Auricular fibrillation and left axis deviation	7		1	1	5
Left axis deviation	39	11	10	9	9
Disturbances of conduction	3	1	2		

Electrocardiography—The analysis of the electrocardiograms obtained for patients suffering from hyperthyroidism does not come within the scope of this paper, but it is interesting to examine briefly the electrocardiographic records of the patients for whom roentgenograms were also made.

In 170 cases an electrocardiogram was taken, in 108 the tracing was normal and usually showed only sinus tachycardia, in 20 cases there was auricular fibrillation, accompanied in 7 cases with deviation of the electrical axis to the left. In 35 cases there was only deviation to the left of the electrical axis, with ventricular extrasystoles in 4 cases and finally in 3 cases, disturbances in the intraventricular conduction.

In table 6 the patients for whom electrocardiograms were made are grouped according to the size of the heart. It can be seen that there

48 Otten²⁵ Kerr and Hensel²⁶ Rosler²⁷ Meyer-Borstel²⁸ Parkinson and Cookson²⁹ Cookson³⁰ Peserico³¹

49 Borak, J. Fortschr. a. d. Geb. d. Röntgenstrahlen **32** 137, 1924

50 Nemet, G. Zur Kenntnis der "Mitralform" gesunder Herzen, Klin. Wchnschr. **2** 348, 1923

were relatively few patients with a normal electrocardiogram among those with an appreciably or greatly enlarged cardiac area and these usually showed auricular fibrillation or deviation to the left of the electrical axis. This is a natural finding, since as has been shown, the majority of the patients with hyperthyroidism in these groups have antecedents of rheumatic fever or also suffer from arterial hypertension or degenerative aortic lesions.

In 64 cases another electrocardiogram was made when the hyperthyroidism had been cured, and it was found that the tachycardia in almost all cases had disappeared. In 9 cases in which there had previously been fibrillation, the sinus rhythm was reestablished, but in the rest of the cases the records did not show any substantial change. In those cases in which there was some disturbance of the intraventricular conduction, the electrocardiogram was not modified.

Thus, there is therefore a suggestive parallel between the electrocardiographic and roentgenographic findings, as both demonstrate the absence of an organic lesion which can be ascribed to hyperthyroidism, since in the cases in which there is modification, usually some other cardiovascular disease is present which can account for it.

SUMMARY

Hyperthyroidism brings about slight or no increase of the cardiac area.

When the cardiac area is increased in a patient suffering from hyperthyroidism, this is due to some cardiovascular disease that is also present.

Recovery from hyperthyroidism is only in a minor number of cases accompanied with reduction of the cardiac area, which to a certain extent is a confirmation of the first two conclusions.

Certain objections may be brought forward and must be discussed.

1 This work is based on the results of teleroentgenograms taken in frontal projection, thus measuring the size of the heart in one plane only. If, however, hyperthyroidism causes some change in the volume of the heart, it is reasonable to think this would be complete and therefore apparent in any plane examined. The possibility that bulging of the left middle arch is due to partial and incipient dilatation has been discarded.

2 Teleroentgenography does not offer an accurate method of measuring the cardiac area, since changes of less than 10 per cent are not registered. Because of this the possibility that the cardiac area may be somewhat enlarged in cases of hyperthyroidism has not been denied.

3 Stewart and Hamilton⁵¹ have asserted that tachycardia causes a decrease in the size of the heart, in which case, since the majority of patients with hyperthyroidism suffer from tachycardia, this would hide the real increase in volume. These authors, however, have only mentioned patients with tachycardia of short duration, and it is unlikely that this conclusion can also be applied in cases of long-standing tachycardia.

4 The patients with moderate cardiac enlargement have not been sufficiently taken into account in formulating the foregoing conclusions. Since in only a fourth of these patients could some other cardiovascular disease be demonstrated, it might be supposed that precisely this moderate enlargement is the result of hyperthyroidism. Definite conclusions, however, are not possible regarding a group of patients with so many doubtful types of conditions.

CONCLUSIONS

Hyperthyroidism per se does not cause enlargement of the cardiac area.

When a patient with hyperthyroidism has an enlarged cardiac area, it must be assumed that this is due to some other cardiovascular disease that is also present.

Hyperthyroidism can cause enlargement of the cardiac area when there is associated cardiovascular disease.

Recovery from hyperthyroidism in such cases may be accompanied with a decrease in the size of the heart, and apart from these cases, recovery from hyperthyroidism is not accompanied with changes in the cardiac area.

The bulging of the left middle arch that is frequently encountered in patients with hyperthyroidism is of constitutional origin and is not a result of hyperthyroidism.

⁵¹ Stewart, H., and Hamilton, C. The Effect of Regular and Irregular Tachycardias on the Size of the Heart, *J Clin Investigation* 3: 483, 1927.

EXOPHTHALMIC GOITER

RELATION BETWEEN THE BLOOD IODINE LEVEL AND THE DURATION
OF SYMPTOMS IN THREE HUNDRED AND FIVE CASES

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AND

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Recent investigations concerning the quantitative estimation of the iodine content of the blood have led to a better understanding of the metabolism of iodine in goitrous conditions. Evidence has been brought forward to show that the iodine level of the blood is elevated in approximately 70 per cent of the cases of clinical hyperthyroidism, in the remaining 30 per cent the level is within the range of normal¹. In former communications² the observation was made that in the greater proportion of cases of hyperthyroidism in which the iodine content of the blood was normal the response to therapy was less favorable than in the cases in which the iodine content was elevated. The duration of hyperthyroidism is recognized clinically as influencing the therapeutic response, in that patients with thyrotoxic symptoms of long standing usually react less favorably to treatment than do those with a history of recent onset of these symptoms. On the basis of the foregoing clinical and laboratory evidence, it seemed reasonable to hypothesize a relation between the concentration of iodine in the blood and the duration of the syndrome of hyperthyroidism. The purpose of the present study was to ascertain whether this supposition was tenable.

METHOD OF STUDY

One must concede that clinical opinion is subject to variation concerning the duration of hyperthyroidism in many cases. For this reason only those cases were included in which there was agreement with

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1 Perkin H J, Lahey, F H, and Cattell, R B. Blood Iodine Studies in Relation to Thyroid Disease. Basic Concept of the Relation of Iodine to the Thyroid Gland, Iodine Tolerance Test, New England J Med **214**:45 (Jan 9) 1936

2 Perkin, H J. The Value of Blood Iodine Estimation in the Diagnosis of Hyperthyroidism, S Clin North America **15** 1625 (Dec.) 1935, The Value of Blood Iodine Estimations in the Treatment of Clinical Hyperthyroidism, *ibid* **16** 1509 (Dec) 1936

respect to the onset of the initial symptoms. In the majority of cases the criteria used to establish the time of onset of the disability were a history of loss of weight, associated with a good appetite, hyperexcitability and irritability, protrusion of the eyes, tremor, palpitation, and dyspnea dating from a known experience. Continued loss of weight following the use of a reducing diet or mental stress due to a specific incident was considered to designate the initiatory phase in a few instances.

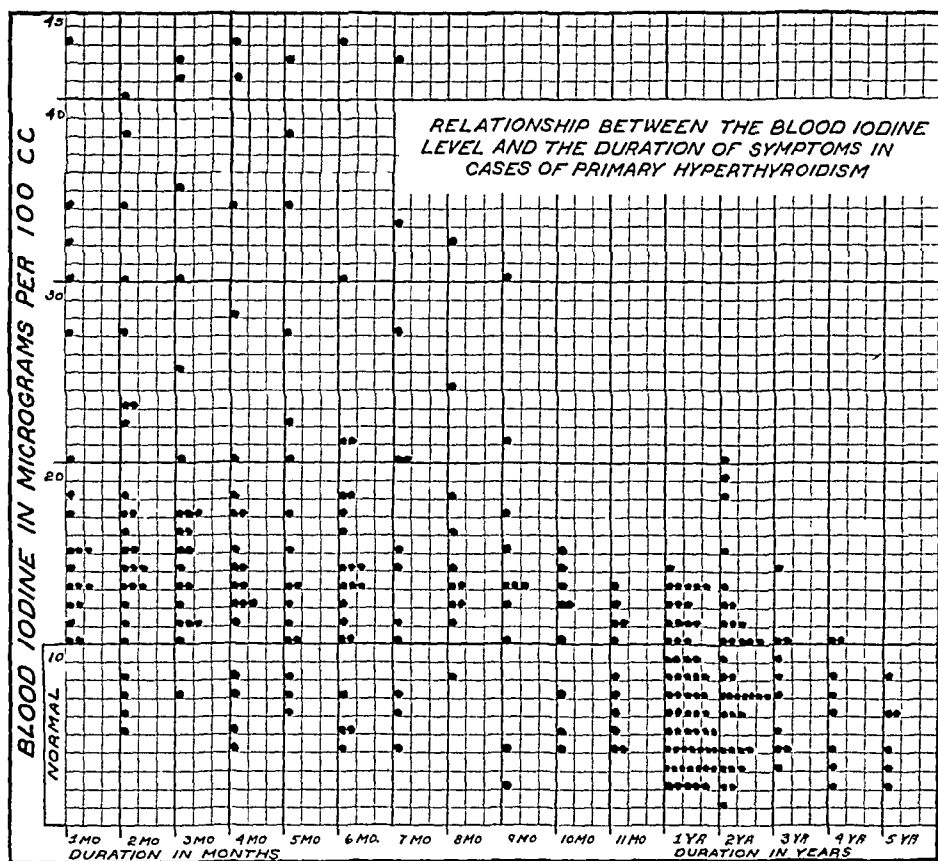


Chart showing the relation between the blood iodine level and the duration of symptoms in 305 cases of primary hyperthyroidism

The series of 305 patients (267 women and 38 men) included in the present report was comprised exclusively of patients with primary hyperthyroidism (exophthalmic goiter). None of the patients, so far as could be determined, had received iodine or other treatment prior to coming under observation at the clinic. The provisional clinical diagnosis of hyperthyroidism was substantiated in every case by basal metabolic tests when the patient was admitted to the hospital and during preoperative medication with iodine, by the histopathologic appearance of the excised thyroid tissue and by examination three months after operation. Before treatment was begun, blood was collected for iodine analysis.

From the data collected, the iodine level of the blood was plotted against the duration of symptoms in individual cases.

RESULTS OF STUDY

Analysis of the results, as shown in the accompanying chart, indicated that the duration of the symptoms of hyperthyroidism varied from one month to five years. Although the distribution of cases was not uniform throughout the entire period, there was considered to be a representative number at each monthly interval to one year and at each yearly interval to five years.

From the accompanying chart it will be seen that of the 163 cases in which symptoms of hyperthyroidism had been present up to nine months, the iodine content of the blood was elevated in 141 (86 per cent) and normal in 22 (14 per cent).³ Approximately half the values fell within the normal range in cases in which the duration of the symptoms was from nine to eleven months. Of the 122 cases in which

Summary of Data

Duration of Symptoms, Months	Number of Cases	Average Basal Metabolic Rate, %	Average Iodine Content, Micrograms, per 100 Cc
1	20	+48	18.8
2	27	+52	18.0
3	22	+50	17.5
4	21	+50	17.0
5	17	+41	15.0
6	22	+45	15.5
7	12	+42	16.0
8	11	+44	14.6
9	11	+47	14.0
10	9	+43	11.0
11	11	+46	9.7
12	60	+45	8.8
24	38	+42	8.7
36	10	+44	8.2
48	8	+38	8.3
60	6	+43	7.4

symptoms of hyperthyroidism had been present for one year or longer, the iodine content was elevated in 36 (29 per cent) and normal in 86 (71 per cent).

The foregoing findings are considered to indicate a tendency for the iodine content of the blood to be within the normal range in cases in which symptoms of hyperthyroidism had been present for one year or longer. The generalization might be drawn that the iodine level decreases as the duration of hyperthyroidism increases. Corroborative evidence in favor of this view is illustrated by averaging the iodine values and the metabolic rates for each group of cases at each time period (table).

As seen in the accompanying table the average basal metabolic rates were roughly within the same range of elevation throughout the

³ According to the methods previously described (Perkin, H. J. Determination of Iodine in Blood, *Biochem. J.* **27** 1078, 1933), 10 micrograms of iodine per hundred cubic centimeters of whole blood is considered to be the upper limit of normal.

entire period. Contrastingly, the average iodine values, which approximated twice normal during the interval of one to four months, fell to a normal level at one year and remained normal throughout the time which followed. The absence of a proportional relation between the degree of elevation of the iodine content and the basal metabolic rate in cases of clinical hyperthyroidism has been noted by others.⁴ That a correlation, however, is present between the iodine level and the duration of symptoms apparently has been overlooked.

COMMENT

Chemical analysis⁵ and histologic examination⁶ of the excised thyroid tissue in cases of hyperthyroidism in which preoperative iodine medication was or was not given have shown that hyperplastic thyroid tissue is deficient in iodine. The recent investigation of Cole and Curtis⁷ has demonstrated the presence of a negative iodine balance in cases of clinical hyperthyroidism. Correlation of the aforementioned studies with the present observations suggests that when the syndrome of hyperthyroidism has been present for one year or longer the iodine content of the blood tends to become normal, in association with a depletion of the iodine reserves of the body.

Since the feeding of thyroid to normal persons effects some of the manifestations characteristic of hyperthyroidism, it is generally assumed that spontaneous hyperthyroidism is related to an excessive amount of secretion from the thyroid gland. In the present study such a view might find application when the iodine level is elevated, as in the cases in which there was a history of short duration. However, it is difficult to conceive that an excessive amount of iodine-containing products is produced by the thyroid gland in cases of hyperthyroidism of long standing when the lack of iodine is evident.

4 Elmer, A. W., and Scheps, M. Iodine Content of Blood and of Urine and Basal Metabolic Rate. Their Value in Diagnosis of Function of Thyroid Gland, *Acta med. Scandinav.* **82**: 126, 1934. Curtis, G. M., Cole, V. V., and Phillips, F. J. The Blood Iodine in Thyroid Disease, *Tr. Am. A. Study Goiter*, 1934, p. 142.

5 Cattell, R. B. The Pathology of Exophthalmic Goitre. Histological and Chemical Study of Changes Following Administration of Iodine (Lugol's Solution), *Boston M. & S. J.* **192**: 989 (May 21) 1925.

6 Marine, D., and Lenhart, C. H. Further Observations on the Relation of Iodine to the Structure of the Thyroid Gland in the Sheep, Dog, Hog and Ox, *Arch. Int. Med.* **3**: 66 (Feb.) 1909. Cattell, R. B. The Relation of Iodine to the Human Thyroid Gland in Certain of Its Pathological States with Especial Reference to the Changes in Exophthalmic Goitre After Lugol's Administration, *Proc. New York Path. Soc.* **25**: 128, 1925.

7 Cole, V. V., and Curtis, G. M. Human Iodine Balance, *J. Nutrition* **10**: 493 (Nov.) 1935.

On the basis of hypersecretion from the thyroid gland manifested in cases in which the iodine content of the blood is elevated, the favorable response to subtotal thyroidectomy is apparent. Further explanation is necessary with regard to a similar response in cases in which the thyroid gland is deficient in iodine and the iodine content of the blood is normal. Since in many cases the syndrome of clinical hyperthyroidism cannot be attributed solely to hypersecretion of iodine-containing products from the thyroid gland, other factors must be considered.

SUMMARY

The iodine level of the blood has been correlated with the duration of the symptoms in 305 cases of primary hyperthyroidism (exophthalmic goiter) in which treatment had not been given.

The iodine level of the blood is elevated in the majority of cases of hyperthyroidism in which symptoms have been present from one to nine months.

The iodine level tends to fall within the normal range when the syndrome of clinical hyperthyroidism has been present for one year or longer.

The theoretical aspects of the present results have been discussed.

PAPILLEDEMA ASSOCIATED WITH SUBARACHNOID HEMORRHAGE

AN EXPERIMENTAL AND CLINICAL STUDY

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AND

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Papilledema occurs in many but not all cases of increased intracranial pressure. Satisfactory criteria have not as yet been established to differentiate between cases of increased cerebrospinal fluid pressure in which papilledema occurs and those in which it does not. Efforts to set up such criteria follow one of two lines. (1) The important factor is the degree of the intracranial hypertension and its duration. (2) The important factor has to do with the mechanism of the production of papilledema.

The present study deals with the occurrence of papilledema in cases of subarachnoid hemorrhage. During the past seven years this diagnosis has been made for eleven patients in the medical wards of this hospital (table 1). In all these cases bloody or xanthochromic spinal fluid was found. In eight cases the pressure was recorded as ranging from 220 to 400 mm of water. In the three other cases readings of the manometric pressure were not obtained, but the pressure was thought to be increased. The eyegrounds have been carefully observed in these cases at intervals after the original attack varying from four days to four years, and in no instance has there been papilledema. We believe that the level of the spinal fluid pressure and the duration of observation have been sufficient for papilledema to have occurred if indeed its appearance depends only on factors of pressure and time.

It has been possible to collect from the literature reports of one hundred and eighteen cases of subarachnoid hemorrhage in which satisfactory ophthalmoscopic examinations were recorded.¹ The disks were

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1 (a) Leopold, S. Spontaneous Subarachnoid Hemorrhage, J A M A 63 1362 (Oct 17) 1914 (b) Neal, J B. Spontaneous Meningeal Hemorrhage, ibid 86 6 (Jan 2) 1926 (c) Symonds, C P. Spontaneous Subarachnoid Hemor-

normal in seventy-eight (66 per cent) of these one hundred and eighteen cases, and papilledema was recorded as definitely present in twenty-four cases (20 per cent). The condition in the remaining sixteen cases (14 per cent) must be regarded as equivocal. They include cases regarding which such statements as the following were made: "There was a faint suggestion of beginning choking at the nasal border of the left disk." "The disks were hazy, probably slightly beyond physiologic limits." In cases in which the findings were listed as equivocal, one must conclude that the authors were uncertain as to whether papilledema was actually present or not. Information with respect to readings of the manometric pressure of the spinal fluid or duration of observation is not adequate to permit analysis of these cases further. However, we have attempted to consider in more detail the cases in which papilledema was definitely

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present, and these will be taken up again later. At this point it may be concluded that (1) papilledema did not occur in our eleven cases, though the degree of elevation of the intracranial pressure and the period of observation appeared adequate, and that (2) it did not occur in a considerable percentage (66 per cent) of the cases reported in the literature.

An experimental approach to the problem was undertaken. It is possible to produce subarachnoid hemorrhage in the rat by thrusting a needle through one of the cranial sinuses. When the skin is retracted, the superior longitudinal and lateral sinuses are visible through the thin skull cap. This method was described in a previous publication on the staining qualities of red blood cells in spinal fluid.² After the

TABLE 1—*Data Concerning Eleven Cases of Subarachnoid Hemorrhage*

Patient No	Age	Sex	Previous Attack	Duration of Observation After Attack	Spinal Fluid	Blood Pressure, Mm Hg	Outcome	Diagnosis Confirmed at Autopsy	Eye grounds
1	29	M	No	8 days	Bloody	122/ 72	Died	Yes	Normal
2	70	M	No	17 days	Xanthochromic	140/ 65	Recovered		Normal
3	44	M	Yes	4 yr	Bloody	125/ 90	Recovered		Normal
4	74	F	No	5 days	Bloody	220/114	Died	No	Normal
5	42	F	No	20 days	Bloody	145/ 90	Died	No	Normal
6	56	M	Yes	10 days	Bloody	186/ 90	Recovered		Normal
7	56	M	No	8 days	Bloody	130/ 90	Died	No	Normal
8	44	M	No	7 days	Bloody	120/ 70	Recovered		Normal
9	45	M	Yes	2 hr	Bloody		Died	Yes	Not examined
9	57	F	No	10 days	Bloody	152/ 90	Recovered		Normal
10	43	M	No	6 days	Bloody	125/ 85	Died	Yes	Normal
11	54	M	No	4 days	Bloody	195/115	Died	No	Normal

production of such a hemorrhage, red blood cells are found in abundance in fluid obtained by cisternal puncture for forty-eight hours or more after the operation.

The rationale of our further experimental procedure is based on work previously reported.³ The principal points may be summarized as follows: 1. Injection of a suspension of colloidal kaolin into the cisterna magna of a normal albino rat causes (a) an increased spinal

² Griffith, J. Q., Jr., Roberts, E., and Jeffers, W. A. Staining Technique for Blood in Spinal Fluid, *J. Lab. & Clin. Med.* **21**: 1208 (Aug.) 1936.

³ Griffith, J. Q., Jr., Jeffers, W. A., and Lindauer, M. A. Study of Mechanism of Hypertension Following Intracisternal Kaolin Injection in Rats, *Am. J. Physiol.* **113**: 285 (Oct.) 1935. Griffith, J. Q., Jr., Jeffers, W. A., Fewell, A. G., and Fry, W. E. Communication and Direction of Flow Between Cerebrospinal Fluid and Optic Discs in the Rat, *Am. J. Ophth.* **20**: 457 (May) 1937. Jeffers, W. A., Griffith, J. Q., Jr., Fry, W. E., and Fewell, A. G. An Experimental Study of Choked Disc in the Rat, *ibid.* **20**: 881 (Sept.) 1937.

fluid pressure, ranging from 260 to 300 mm of water, as compared with the normal of less than 100 mm, and (b) a vascular hypertension of 170 to 300 mm of mercury, as compared with a normal blood pressure of less than 150 mm

2 Such rats, called for convenience kaolin-hypertensive rats, show no changes in the fundus on ophthalmoscopic or slit lamp examination or on histologic section of the eye

3 If colloidal thorium dioxide is injected into the cisterna magna of a normal rat, in thirty minutes it can be seen roentgenographically (a) in the cervical lymph nodes and (b) along the optic tracts and nerves after decapitation and after decalcification of the skull. On histologic examination it is found to lie in the perineural space of the optic nerve

4 If thorium dioxide is injected into the cisterna magna of a kaolin-hypertensive rat, it does not pass in sufficient quantities to appear in roentgenograms taken either of the cervical lymph nodes or of the optic nerves but remains indefinitely in the cerebrospinal space and ventricles, where it is visible roentgenographically. On histologic study it is either absent from the perineural space of the optic nerve or present in greatly diminished quantity

5 If a sarcoma is implanted successfully into the cerebellum of a normal rat, changes will occur in the eyes as follows (a) On ophthalmoscopic examination the veins are greatly distended, and there is a suggestion of edema of the disk. This is difficult to evaluate because of the absence of pigment in the albino and, in addition, because the frequent corneal haze makes examination difficult (b) By slit lamp examination of the enucleated eye with the contents removed the elevation of the disk is confirmed (c) By histologic section the venous engorgement and the appearance of edema are confirmed. This condition is thought by us to correspond to papilledema in man

6 When a similar tumor is implanted into a kaolin-hypertensive rat, no fundal changes occur

We have therefore concluded that kaolin in the cerebrospinal space (1) blocks the passage of thorium dioxide along the perineural space of the optic nerve and (2) prevents the occurrence of fundal changes even in the presence of a growing tumor of the brain. We believe the evidence justifies the assumption that, at least in the rat, papilledema cannot occur if the perineural space is not patent and that a test for this patency is the ability of thorium dioxide, introduced into the cistern, to enter this perineural space in considerable amounts. We believe that red blood cells in the cerebrospinal fluid might act like kaolin in blocking the perineural space

EXPERIMENTAL METHOD

Twenty normal albino rats were used. With the animal under ether anesthesia, a small trephine opening was made over the superior longitudinal sinus. A fine needle was inserted through the sinus to a depth of about 2 mm and withdrawn. Free external bleeding occurred. Six of the animals had a single subarachnoid hemorrhage, while fourteen had three hemorrhages at three day intervals. Ophthalmoscopic examination was made at intervals. All were finally given an intracisternal injection of thorium dioxide, six at the end of the fourth day and fourteen at the end of the tenth day. The thorium dioxide was given as follows: With the animal under ether anesthesia, cisternal puncture was performed, and 0.05 cc of spinal fluid was withdrawn. An equal amount of thorium dioxide was injected. At the end of twenty-four hours the animal was killed and decapitated. The head was cleaned and placed in 3 per cent hydrochloric acid for three days. Roentgenograms were then taken.

EXPERIMENTAL RESULTS

Ophthalmoscopically, the fundi were normal. The results of the roentgenographic study are shown in table 2. We know that all the

TABLE 2—*Data Concerning Twenty Rats in Which Experimental Subarachnoid Hemorrhage Was Induced, Followed by an Intracisternal Injection of Thorium Dioxide*

Procedure	Number of Animals	Number with Optic Nerves Visualized	Number with Optic Nerves Not Visualized
One subarachnoid hemorrhage	6	2	4
Three subarachnoid hemorrhages	14	3	11
Totals	20	5	15

injections were successful, because the thorium dioxide could be seen about the cerebellum. In only five cases, however, did it pass to the optic nerves. In twenty normal animals the thorium dioxide would have been seen about the optic nerves in every case.

Figure 1 *A* is a roentgenogram of the decalcified skull of a rat that had received no thorium dioxide. Figure 1 *B* is a roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally one hour before death. Note the fine lines of thorium dioxide about the cerebellum and the optic nerves (indicated by arrows). Figure 2 is a roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally twenty-four hours before death. This rat had three subarachnoid hemorrhages at three day intervals, the last one being induced four days before the injection of thorium dioxide. Lines of thorium dioxide appear about the cerebellum and about the olfactory nerves but not about the optic nerves.

Figure 3 is a photomicrograph of the perineural space of the optic nerve of a rat twenty-four hours after experimental subarachnoid hemorrhage. The space contained many red blood cells.

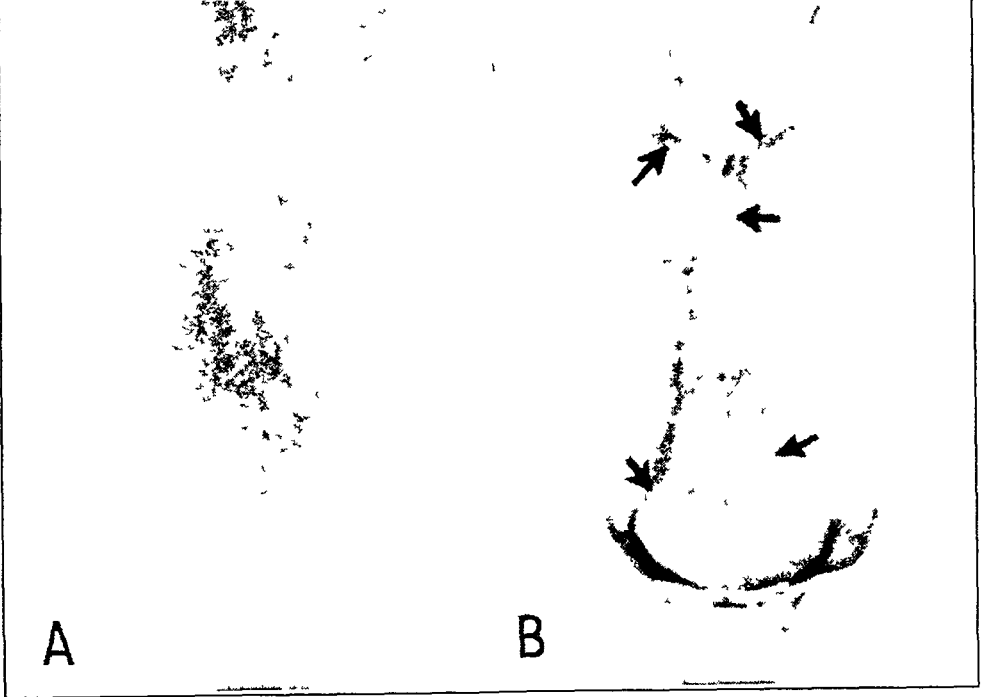


FIG 1—*A*, roentgenogram of the decalcified skull of a rat that had not received thorium dioxide. *B*, roentgenogram of the decalcified skull of a rat given thorium dioxide intracisternally one hour before death. Lines of thorium dioxide about the cerebellum and along the optic nerves are indicated by arrows.

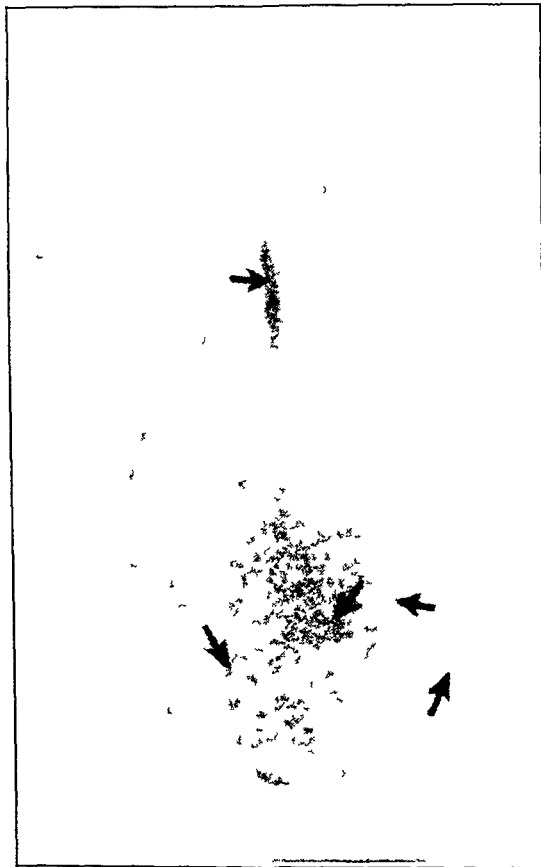


FIG 2—Roentgenogram of the decalcified skull of a rat given thorium dioxide twenty-four hours before death. This rat had three subarachnoid hemorrhages. Lines of thorium dioxide about the cerebellum and along the olfactory nerves are indicated by arrows. The optic nerves are not shown.

COMMENT

The evidence presented suggests that red blood cells in the cerebrospinal fluid can block the perineural space of the optic nerve to thorium dioxide exactly as does kaolin though not as consistently. Although the manipulation was identical in all cases, the amount of blood which actually entered the cerebrospinal space may have varied widely. If the block were a physical one, depending on the number of red blood cells, we would anticipate that it would not be complete in

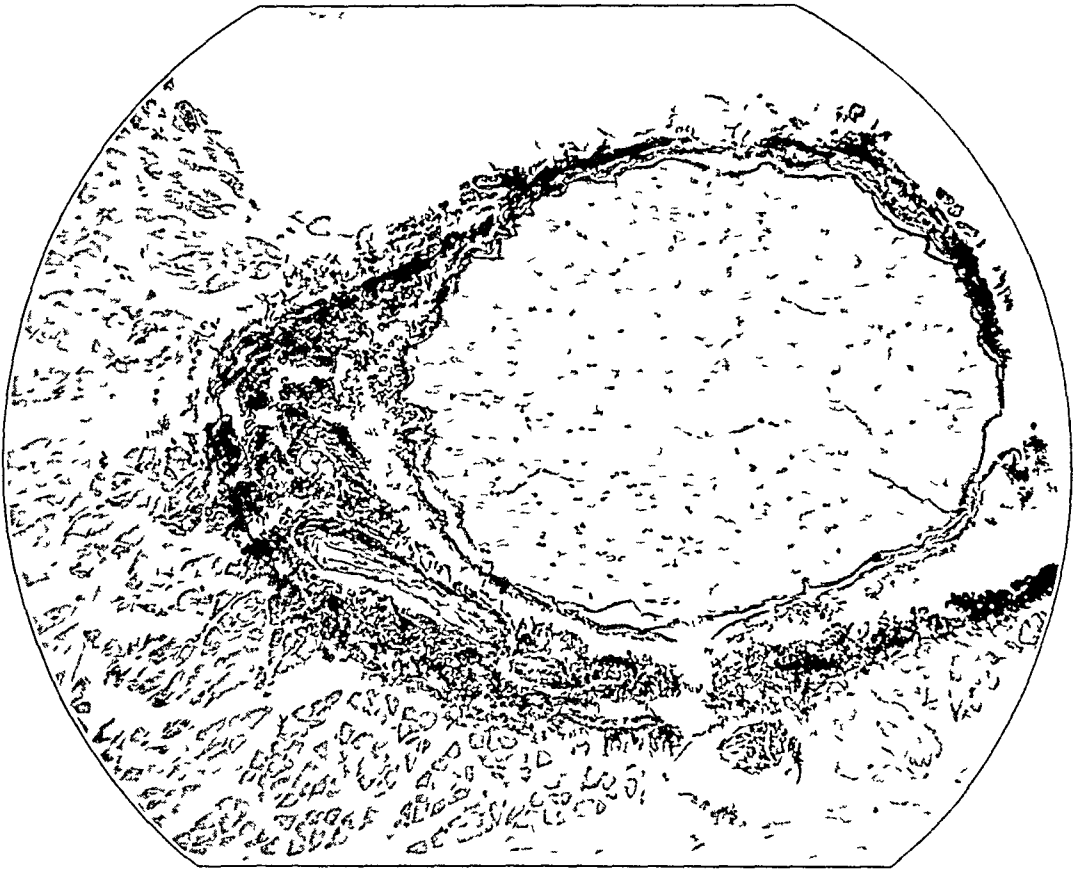


Fig 3—Photomicrograph of the perineural space of the optic nerve of a rat twenty-four hours after experimental subarachnoid hemorrhage. The space contains many red blood cells.

all cases. In line with this thought is the evidence that block is more often complete in cases in which there have been three hemorrhages than in those in which there has been one, though the series is too small to make this absolutely certain.

If, based on the evidence previously described, the patency of the perineural space of the optic nerve to thorium dioxide indicates the ability to acquire papilledema, we might expect that in fifteen of our twenty animals with subarachnoid hemorrhage choked disk could not

have developed even if added factors which ordinarily cause choking had been present. On the other hand, we might expect that in five of our twenty animals papilledema would have developed if other factors which ordinarily produce choking had been present coincidentally.

In reviewing further the twenty-four cases of subarachnoid hemorrhage with definite papilledema reported in the literature, we find the following data: 1. The blood pressure was high in ten cases. In three of these the diagnosis was confirmed at autopsy. 2. The blood pressure was normal in one case, the diagnosis being confirmed at autopsy. 3. The blood pressure was not given in thirteen cases. In seven of these there was no autopsy. In the six cases in which autopsy was performed the diagnosis was confirmed in three, in two cases glioma was found and in one case there was a large unruptured aneurysm which was thought to have acted like a tumor.

It appears to be rare for definite papilledema to occur in a case of proved uncomplicated subarachnoid hemorrhage. Among the complications which might occur and cause papilledema are (1) a hemorrhage largely into the ventricles, with only a little blood reaching the subarachnoid space, (2) malignant hypertension, (3) glioma and (4) sinus thrombosis.

REPORT OF CASES

Hemorrhage into the Ventricles—Cookson^{1w} has reported the case of a man of 32 who had an attack of headache, pain in the neck and vomiting on July 4, 1924. He remained in bed two weeks, when he again vomited, became unconscious and was taken to the hospital. When admitted he was semiconscious and irritable. There was palsy of the right facial nerve and an extensor plantar reflex on the right side. Cervical rigidity and a definite Kernig sign were noted. The cerebrospinal fluid was blood stained. The fundi oculi were normal on entry, but shortly afterward papilledema appeared in both eyes and later became severe. He improved somewhat, but eleven days after admission to the hospital he suddenly went into a coma and died the next day. At autopsy a blood clot was seen adherent to the left internal carotid artery at the point of its bifurcation. In this region the brain tissue was ploughed up, and blood clot filled the left lateral, third and fourth ventricles.

Cerebral Hemorrhage Involving the Subarachnoid Space in the Course of Malignant Hypertension—The patient, a Negro 45 years of age, had been well until five years prior to admission to the hospital. At that time he was told he had high blood pressure, the systolic pressure being 240 mm. He continued in fair health until two years before admission to the hospital, when he noted some failing of vision. About this time he began to have attacks of unconsciousness, lasting about five minutes, which recurred irregularly but on the average of about once a month. Some convulsive movements during an attack were described by his wife. However, the attacks were always of short duration, and he recovered rapidly, never requiring hospitalization. His physician stated that for at least a year prior to admission to the hospital he had definite bilateral papilledema.

On the day of entry the patient suddenly had a generalized convulsion, lost consciousness and was admitted to this hospital in coma, which persisted until his

death The blood pressure was 260 systolic and 160 diastolic The pupils did not react to light The fundus of the right eye showed numerous old and new hemorrhages and fairly marked evidence of angiosclerosis The disk showed definite slight papilledema The fundus of the left eye was similar Spinal puncture, thrice repeated, revealed bloody fluid under increased pressure The patient died two days after admission to the hospital At autopsy a cerebral hemorrhage was seen involving the right occipital lobe, with blood in the subarachnoid space The right ventricle was dilated and filled with blood The bleeding point could not be ascertained

Subarachnoid Hemorrhage Complicated by a Glioma (reported by Laurent¹¹) — A man aged 26 was admitted to the hospital on April 11, 1931 For two weeks he had complained of headache and vomiting On April 7 he vomited and lost consciousness Violent convulsive movements of the right arm occurred, while the left limb and left side of the face seemed to be paralyzed He recovered to some extent but remained stuporous

On entry he was comatose, and the temperature was 100.6 F The fundus oculi bilaterally showed papilledema There were cervical rigidity, a definite Kernig sign and flexor plantar responses The cerebrospinal fluid was evenly blood stained The next day he recovered sufficiently to enjoy an illustrated magazine On April 13 he again became comatose and died Necropsy revealed a large hemorrhage originating from a glioma and reaching the surface of the frontal lobe

Sinus Thrombosis and Subarachnoid Hemorrhage (reported by Byers¹²) — A girl aged 1 year who had previously been healthy began to vomit on Oct 16, 1931 The next day a physical examination showed no abnormality Diarrhea developed Two days later there were convulsive twitchings of the right arm, followed by generalized convulsions She then appeared to improve, but on the eleventh day of her illness she was drowsy and irritable The following day there were rhythmic convulsive movements of the legs and rigidity of the neck, back and extremities The spinal fluid was xanthochromic and under increased pressure Generalized convulsions soon developed Within a few hours engorgement of the facial veins, edema of the left eyelids and a bulging fontanelle became evident The eyegrounds showed edema of the optic disks and congestion of the retinal veins Convulsions continued, and death occurred on the fourteenth day At necropsy there was seen in the superior longitudinal sinus a thrombus with extensions into the contiguous sinuses and veins

SUMMARY

Papilledema did not occur in any of the eleven cases of subarachnoid hemorrhage studied, although the elevation of the spinal fluid pressure and the duration of observation appeared adequate In seventy-eight (66 per cent) of the one hundred and eighteen cases reported in the literature papilledema did not develop In this series, the findings in sixteen cases (14 per cent) were equivocal, while in twenty-four cases (20 per cent) definite papilledema developed In seven of these twenty-four cases the diagnosis was confirmed at autopsy, and in three of these cases hypertension was known to have been present In two other cases glioma of the brain was found, and in one case a large unruptured aneurysm was thought to have acted like a tumor

In previous work it was shown that kaolin injected intracisternally into rats (1) prevented the passage of thorium dioxide, injected intracisternally, along the perineural spaces of the optic nerves and (2) prevented the appearance of papilledema in the presence of a growing cerebellar tumor. After experimental subarachnoid hemorrhage, thorium dioxide was blocked from entering the perineural spaces of the optic nerves in fifteen of twenty rats. It was therefore inferred that blood in the spinal fluid if present in sufficient amount tends to block the perineural spaces of the optic nerves and prevent the development of papilledema. In a minority of cases, however, the block is incomplete, and papilledema may occur if other predisposing factors are present. Among these factors are (1) a partial ventricular block, so that relatively little blood reaches the subarachnoid space, (2) malignant hypertension, (3) glioma and (4) sinus thrombosis. Illustrative cases are cited.

COEXISTENCE OF BRONCHIECTASIS AND SINUSITIS

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The frequent coexistence of bronchitis and bronchiectasis with sinusitis has been recognized since the publication of the reports of Rist¹ and Sergent,² and confirmation of their observations has been offered repeatedly. This association is well known to otolaryngologists, but appreciation by general practitioners and specialists in other fields has lagged surprisingly. The relation between the disease of the upper and that of the lower respiratory tract is more than coincidental in the opinion of most observers. Whether the sinusitis precedes, follows or develops simultaneously with the bronchitis is not settled. The prevailing concept is that sinusitis and bronchitis probably develop simultaneously during an acute infection, such as influenza. Mullin³ gave as his opinion that patients with bronchitis tend to get well unless the condition is fostered and fed by a chronic sinus infection. This appears to be logical. Rist¹ compared the respiratory tract to the urinary tract, in which cystitis follows renal infection. Mullin³ offered as explanation for the concomitant lesions the repeated aspiration of infective material into the bronchi from the upper respiratory tract. He objected to the concept of infection spreading from the bronchi to the sinuses because there is no ready route and because of the great number of patients, especially children, with cough and moist rales at the bases

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1 Rist, E. Le principes du diagnostic rationnel de la tuberculose pulmonaire, *Presse med* **24** 305, 1916, Les diagnostic differentiel de la tuberculose pulmonaire et les affections chroniques des fosses nasales, *ibid* **24** 321, 1916

2 Sergent, E. Histoire suggestive de quelques faux tuberculeux, diagnostic differentiel de la tuberculose pulmonaire et des affections des voies respiratoires superieures, *Bull et mem Soc med d hôp de Paris* **40** 1424, 1916, Considerations sur la statistique du centre de triage, la Charité le Vesinet, de Juin 1916 à Decembre 1917, *J de med et chir prat* **89** 643, 1918

3 Mullin, W V. The Accessory Sinuses as an Etiologic Factor in Bronchiectasis, *Ann Otol, Rhin & Laryng* **30** 683, 1921. A Review of Sinus-Chest Infections, *ibid* **41** 794, 1932

of the lungs who get well after early diagnosis of the condition and treatment of the sinuses Wasson and Waltz⁴ drew similar conclusions from roentgen findings for children with sinus infection and pulmonary disease

In experimental animals Mullin and Ryder⁵ demonstrated aspiration of ink and suspensions of tubercle bacilli from the nares and the antrum into the bronchial tree After the introduction of india ink they observed black spots all along the respiratory tract post mortem, with discoloration of the bronchial nodes and of the lungs Aspiration of tubercle bacilli resulted in tuberculosis of the lungs Involvement of the lungs followed instillation of the bacilli or india ink into the antrum, even though egress to the nares was prevented This was explained on the basis of a lymphatic and venous route to the right side of the heart and then to the lungs Corper and Robin⁶ confirmed and amplified these results in their study of dogs and rabbits

Quinn and one of us (Dr Meyer)⁷ ascertained that when iodized oil was passed through a catheter just into the anterior nares of a sleeping individual, the oil, often in large quantities, was demonstrable roentgenographically in the bronchi or in the pulmonary parenchyma the next morning⁷ This experiment has been confirmed and the conclusion accepted⁸ The ease and regularity of the occurrence led to the conclusion that aspiration of pus probably occurs with similar facility Consequently, it was thought likely that this was the most important explanatory factor for the frequent concomitance of sinusitis and bronchiectasis Incidentally, this circumstance emphasized the importance of treatment of sources of pus, the sinuses, as well as treatment of the bronchi in cases of chronic bronchitis and bronchiectasis

The frequency of sinusitis in association with infection of the bronchi varies with different reports Thus, Kistner⁹ found sinusitis in all but 6 of 196 cases of chronic nontuberculous bronchitis Dunham

4 Wasson, W W, and Waltz, H D The Relationship of Sinus Disease to Chest Disease in Children, *Radiology* **22** 432, 1934

5 Mullin, W V, and Ryder, C T Studies on the Lymph Drainage of the Accessory Nasal Sinuses, *Laryngoscope* **31** 158, 1921 Mullin, W V Lymph Drainage of the Accessory Nasal Sinuses, *ibid* **29** 606, 1919

6 Corper, H J, and Robin, H A The Pulmonary Aspiration of Particulate Matter, *Am Rev Tuberc* **6** 813, 1922

7 Quinn, L H, and Meyer, O O The Relationship of Sinusitis and Bronchiectasis, *Arch Otolaryng* **10** 152 (Aug) 1929

8 Meakins, J C Practice of Medicine, St Louis, C V Mosby Company, 1936, p 148

9 Kistner, F B Infections of Accessory Nasal Sinuses as the Cause of Chronic Non-Tuberculous Bronchitis, *Northwest Med* **26** 203, 1927

and Skavlem¹⁰ found sinusitis coexisting in 73 per cent of 26 cases of bronchitis. McLaurin¹¹ said he believed that the association of bilateral bronchiectasis and paranasal sinus disease is almost constant. Hodge¹² reported associated sinusitis in 75 per cent of his 37 cases. Meiks,¹³ in a study of children, found sinusitis present in 81 per cent of those with bronchiectasis. Quinn and one of us (Dr Meyer)⁷ reported that 22 of 38 patients with bronchiectasis (57.9 per cent) had coexistent sinusitis. The fact was emphasized that the majority of the patients had no symptoms of sinusitis. Kern and Schenck,¹⁴ in a controlled series, found that sinusitis existed less frequently in patients with no history of susceptibility to colds, recent infection of the respiratory tract or frank sinus disease in the past than in patients with bronchiectasis.

The present study was made in order to amplify the study of 38 patients which was reported in 1929.⁷ It is now possible to report on the incidence of sinusitis in a total of 217 patients with bronchiectasis admitted to the State of Wisconsin General Hospital between 1925 and 1936, exclusive of patients with congenital bronchiectasis or with bronchiectasis due to foreign body. (One of the 38 cases reported on in 1929 was due to aspiration of a foreign body, the remaining 37 are included in the total number of this report.) It may be stated that in this report as in the previous report, sinusitis was diagnosed only when gross pus was demonstrable in one or more of the paranasal sinuses.

On analysis of this group of 217 patients, it was found that 145 (66.8 per cent) had associated sinusitis. This figure closely approximates the incidence of 57.9 per cent in the first 38 patients studied.

A study of these 145 patients showed that 84 (58 per cent) were males, and 61 (42 per cent) were females. The oldest patient was 78 and the youngest 6 years old. The average age at the time of admission to the hospital was 32.4 years and the average age at the onset of symptoms 26.1 years. However, 49 per cent of the patients admitted

10 Dunham, K., and Skavlem, J. H. Chronic Non-Tuberculous Infections. *U. S. Vet. Bur. M. Bull.* **3**: 861, 1927.

11 McLaurin, J. G. Chest Complications of Sinus Disease, *Ann. Otol., Rhin. & Laryng.* **41**: 780, 1932, A Review of the Interrelationship of Paranasal Sinus Disease and Certain Chest Conditions, with Especial Consideration of Bronchiectasis and Asthenia, *ibid.* **44**: 344, 1935.

12 Hodge, G. E. Relation of Bronchiectasis to Infection of Paranasal Sinuses, *Arch. Otolaryng.* **22**: 537 (Nov.) 1935.

13 Meiks, L. T. Study of Bronchiectasis with Reference to Its Etiology and Management, *Tr. Am. Laryng., Rhin. & Otol. Soc.* **41**: 421, 1935.

14 Kern, R. A., and Schenck, H. P. Chronic Paranasal Sinus Infections: Relation to Diseases of Lower Respiratory Tract, *Arch. Otolaryng.* **18**: 425 (Oct.) 1933.

were under 25, and 66.8 per cent were under 40. In 64.8 per cent of the patients the onset of the disease occurred before the age of 30 years. It is noteworthy that in 31 cases the onset antedated the age of 5, although none of the patients in this series was under this age.

Various symptoms and illnesses preceded the apparent onset of the bronchiectasis. In 73 (half the cases) the anamnesis did not permit conclusions as to the possible exciting cause. In 22 of the remaining 72 cases (30.6 per cent) the onset dated from influenza and in 19 (26.4 per cent) from pneumonia. However, the incidence of influenza and pneumonia in the past medical history was greater, although the patients did not relate the symptoms to these illnesses on entry.

The bronchiectasis involved both lungs in 109 cases (75.2 per cent), and the bases alone were involved in 99 (68.3 per cent) of these. In 72 cases (49.7 per cent) the bases were equally involved, in 21 (14.6 per cent) the base of the left lung showed greater involvement than that of the right, while in 6 cases the base of the right lung showed the more extensive disease. In the remaining 36 cases there was unilateral involvement, and as in the original study of 38 cases, there was no predominance of disease of the right lung over that of the left. Thus, involvement of the right and of left lung each occurred in 18 cases (12.4 per cent). This is in direct variance with the common opinion that disease of the right lung occurs more frequently and is more severe.

The degree of bronchiectasis was based on the subjective and objective symptoms, the general constitutional disability, the roentgen findings and, in 5 instances, the postmortem observations. It must be admitted that differences of opinion might here occur in some borderline cases. In 42 cases (29 per cent) there was only mild bronchiectasis, in 81 cases (55.8 per cent), moderately advanced disease, and in 22 cases (15.2 per cent), far advanced disease. Satisfactory filling of the bronchi with iodized oil was possible in 100 of the 145 cases, and roentgenography following this aided in establishment of the existence and of the degree of the disease.

The extent of sinus involvement was variable, and no relation between the degree of sinusitis and the degree of bronchiectasis was established. Chronic pansinusitis or gross bilateral infection of the antrum was found to exist in 78 cases (53.8 per cent).

Satisfactory bacteriologic studies were not always made. However, repeated examinations of sputum for tubercle bacilli were made in 135 of the cases, and the organisms were found in 1 case. The predominant organism in the sputum was not reported in two thirds of the cases, in the remaining cases streptococci predominated, being present in 28 cases. Vincent's organisms were not found in the sputum in 8 of the 10 cases in which they were sought.

Summary of Data

	Bronchiectasis			
	With Sinusitis		Without Sinusitis	
	Number	Percentage	Number	Percentage
Cases	145	66.8	72	33.2
Males	84	58	41	57
Females	61	42	31	43
Average age on entry	32.4 years		35 years	
Under age of 25 years	71	49.0	26	36.1
Under age of 40 years	97	66.8	43	59.7
Average age at onset	26.1 years		27.5 years	
Type of onset (from history)				
Unknown	73	50.4	29	40.3
Influenza	22	15.1	7	9.7
Pneumonia	19	13.1	19	26.4
Influenza and pneumonia			2	2.8
Common cold	14	9.6	7	9.7
Grip	4	2.8		
Sinus infection	2	1.4		
Measles	1	0.7		
Mumps	1	0.7		
Scarlet fever	1	0.7		
Pertussis	2	1.4		
Diphtheria	1	0.7	1	1.4
Typhoid	1	0.7		
Pleurisy	1	0.7	1	1.4
Weakness and fever	1	0.7		
Shortness of breath	1	0.7		
Exposure	1	0.7		
"Spitting up blood"			2	2.8
Chill followed by sweating			1	1.4
Asthma			1	1.4
Childbirth			1	1.4
Type of bronchiectasis				
Bilateral	109	75.2	38	52.8
Right lung	18	12.4	19	26.4
Left lung	18	12.4	15	20.8
Severity of bronchiectasis				
Slight	42	29.0	23	32.0
Moderately advanced	51	55.8	35	48.6
Far advanced	22	15.2	14	19.4
Filling of bronchi with iodized oil				
Satisfactory	109	69.0	42	58.3
Inadequate	8	5.5	4	5.6
None	37	25.5	26	36.1
Disease of respiratory tract in past				
Influenza	35	24.1	13	18.0
Pneumonia	30	20.7	19	26.3
Pleurisy	4	2.8	1	1.4
Pertussis	6	4.1	2	2.8
Combination of 2 or more diseases	33	22.8	27	37.5
None	37	25.5	10	14.0
Tonsils				
Septic	56	38.6	33	45.8
Atrophic	18	12.4	12	16.7
Tags	8	5.5	6	8.4
Removed	55	38.0	17	23.6
Condition unknown	5	3.4	2	2.8
Normal	3	2.1	2	2.8
Predominating organisms in sputum				
Unknown	99	68.3	42	58.4
Streptococci	23	19.3	17	23.3
Yeast	6	4.1	1	1.4
Fungi	4	2.8	2	2.8
Spirochetes and fusiform bacteria	2	1.4	3	4.2
Gram positive bacilli	1	0.7		
Streptothrix			1	1.4
Gram positive diplococci			1	1.4
No tubercle bacilli	135	93.1	65	90.3
Tubercle bacilli	1	0.7	2	2.8
Not examined	9	6.2	5	6.9
No fungi	20	13.8*	5	6.9
No spirochetes or fusiform bacilli	8	5.6	7	9.7

* This figure includes some cases of bronchiectasis with sinusitis and all without sinusitis in the foregoing figures

Summary of Data—Continued

Type of sinusitis	Bronchiectasis			
	With Sinusitis		Without Sinusitis	
	Number	Percentage	Number	Percentage
Pansinusitis	39	26.9		
Bilateral maxillary and ethmoid	8	5.5		
Bilateral maxillary and frontal	6	4.1		
Bilateral maxillary and sphenoid	1	0.7		
Bilateral maxillary, right ethmoid and sphenoid	1	0.7		
Bilateral maxillary and right ethmoid	3	2.1		
Right antrum and frontal	2	1.4		
Bilateral maxillary and left frontal	2	1.4		
Bilateral maxillary and right frontal	1	0.7		
Left antrum, left ethmoid and frontal	1	0.7		
Left antrum and frontal	1	0.7		
Bilateral maxillary	39	26.9		
Right frontal and right antrum	1	0.7		
Left antrum, right ethmoid	1	0.7		
Right antrum and right sphenoid	1	0.7		
Right antrum	18	12.4		
Left antrum	13	9.0		
Right frontal	4	2.8		
Left frontal	1	0.7		
Left ethmoid	1	0.7		
Unknown	1	0.7		

In 72 (33.2 per cent) of the 217 patients there was no evidence of sinusitis. As in the group with sinusitis, there was a slight predominance of males, the ratio being 57 to 43. The average age in this group at the time of entry was somewhat higher, 35 years, the range, 8 to 73 years. The average age at onset was also higher, 27.5 years. Twenty-six (36.1 per cent) of the patients were under 25 at the time of admission to the hospital, and 43 (59.7 per cent) were under 40. A significant number of patients—31 (43 per cent)—were under 20 years of age at the time of onset of the disease.

Most of these patients ascribed the onset of bronchiectasis to definite disease or symptoms. Twenty-nine (40.3 per cent) could relate the disease to no cause. Of the remaining 43 patients, 19 (44.2 per cent) dated their illness from pneumonia, whereas only 7 (16.3 per cent) had had preceding influenza. Only 14 per cent of the patients failed to give a history which included disease of the respiratory tract at some time in the past.

Both lungs were involved in 38 (52.8 per cent) of the cases of bronchiectasis without sinusitis, a distinctly lower frequency than in the group of cases of bronchiectasis with sinusitis. In the 34 cases of unilateral bronchiectasis without sinusitis the right lung was involved 19 times and the left lung 15 times.

The degree of bronchiectasis was mild in 23 cases (32 per cent), moderately advanced in 35 (48.6 per cent) and far advanced in 14 (19.4 per cent). Postmortem examination was made in 7 of these cases of bronchiectasis without sinusitis. Satisfactory filling of the bronchi with iodized oil was possible in 42 of the 72 cases.

Examination of the sputum for tubercle bacilli was made in 65 of the 72 cases and showed positive results twice. In 17 of the 30 cases in which the predominating organism in the sputum was reported, it was found to be the streptococcus.

A comparison of the two groups of cases of bronchiectasis (with and without sinusitis) is afforded by study of the accompanying table.

COMMENT

Study of these results reemphasizes the frequency of sinusitis in association with bronchiectasis. The ease of aspiration of iodized oil from the nares by a recumbent sleeping person makes the factor of repeated infection of the bronchi, which would otherwise heal, by aspiration of pus seem logical. The frequent history of preceding influenza and pneumonia suggests that the bronchi and sinuses may well be infected simultaneously. The cases of bronchiectasis without sinusitis, however, were commonly preceded by influenza, pneumonia or some other infection of the respiratory tract. Consequently, it must be appreciated that bronchiectasis can occur without gross infection of the sinuses. That sinusitis may have previously existed or may have persisted in minimal degree cannot be excluded. Furthermore, disease elsewhere in the upper respiratory tract, as for example in the tonsils, may operate to reinfect the bronchi. Nevertheless, the importance of the sinus infection is not to be minimized, and the opinion is held that in early bronchitis, if disease of the sinuses is recognized and treated, bronchiectasis may, at least occasionally, be prevented. It is well recognized that treatment of the sinuses as well as treatment of the lower respiratory tract is imperative in bronchiectasis if good results are to be obtained.

The relative frequency of bronchiectasis in children is again brought out in this study. The association of sinusitis in this group is especially common, and early recognition and treatment of the sinuses may be of greatest benefit.

Finally, the lack of symptoms of sinusitis in most of the cases here reported is of importance, indicating the need for careful exclusion of disease of the upper respiratory tract by roentgenograms and other available means.

SUMMARY AND CONCLUSIONS

One hundred and forty-five (66.8 per cent) of 217 patients with bronchiectasis were found to have associated sinusitis.

The majority of these patients had no subjective symptoms of sinusitis.

As a class, the patients with sinusitis were younger than those without.

From this series no definite relation between the degree of sinusitis and the degree of bronchiectasis could be established

Contrary to general opinion, in cases of bilateral bronchiectasis there was no demonstrable predominance of disease of the right lung, and in cases of unilateral bronchiectasis there was no greater incidence of involvement of the right lung

It is believed that the relation between sinus disease and disease of the lower respiratory tract is more than coincidental and that drainage from the sinuses, especially when the patient is recumbent and asleep, makes for repetitive infection of the bronchi

The importance of early diagnosis and treatment of existing sinus disease in cases of bronchitis and bronchiectasis is emphasized

ANEURYSM OF THE INNOMINATE ARTERY

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Within recent years, particularly since the development of methods for the intensive treatment of syphilis, aneurysms of the large vessels, on the whole, have not been of as much clinical interest to physicians and students as formerly. Recently a patient with aneurysm of the innominate artery was under my observation. This case perhaps illustrates the potential danger to the patient of vigorous antisyphilitic treatment in association with aneurysm, with its resultant subjective improvement, and also may serve as a gentle reminder that clinicians in the past were thoroughly familiar with aneurysm of this type, that they developed methods of treating such an aneurysm which often were successful and that past experience may well serve as a guide toward improving in the future the methods of treatment when an aneurysm involves this particular vessel.

Curiously, aneurysms of the innominate artery are by no means common. According to Osler¹ and Reid and Andrus,² they represent only about 3 per cent of all internal aneurysms. Yet because of their spectacular appearance and course, they have interested clinicians for centuries.

It is said that the earliest mention of aneurysm of the innominate artery in medical literature was made by Antyllus,³ a surgeon who lived in the middle of the second century A D. Ambroise Paré⁴ (1510-1590) was the first to suggest the causative relation of syphilis and aneurysm, in his famous report of a tailor who while playing tennis "fell dead, the vessel being broken, such as frequently happens to those who have often had the unction and sweat for the cure of the French Disease," and the clinical diagnosis of ruptured aneurysm was confirmed at a public anatomic demonstration by Paré himself.⁵ The story is told of Valsalva,

From the Evans Memorial for Clinical Research and Preventive Medicine

1 Osler, W. Aneurysm, in *Modern Medicine*, Philadelphia, Lea & Febiger, 1908, vol 4, chap 11, p 448

2 Reid, M R, and Andrus, W. Surgery of the Arteries, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1931, vol 1, chap 12, p 752

3 Antyllus, cited by Osler¹

4 Paré, cited by (a) Beekman, F. Studies in Aneurysm by William and John Hunter, *Ann M Hist* 8 126 (March) 1936 (b) Major, R W. Classic Descriptions of Disease, Springfield, Ill, Charles C Thomas, Publisher, 1932, p 417

5 Paré, cited by Fitz, R. A Case of Thoracic Aneurysm, *M Clin North America* 16 863 (Jan) 1933

an Italian physician of the eighteenth century, that he cured patients with aneurysm by starving them. According to Matas,⁶ Valsalva once was holding a clinic at Imola on the medical treatment of aneurysm. A poor patient with a large aneurysm of the neck, probably of the innominate or the carotid artery, was one of the subjects of the lecture. The man listened attentively when Valsalva said that in some cases aneurysm can be cured by diet and rest, provided the patient can endure the hardship of treatment. Little sips of water, a few spoonfuls of claret, a dry crust of black bread and a bit of dry meat now and then—just enough to keep body and soul together—with rest flat in bed, that would cure aneurysm in the right sort of case. About six months later Valsalva was surprised to have an emaciated man come and kneel down before him and kiss his coat. Valsalva said, "What is the matter?" To which the patient replied, "Why, don't you know you have saved my life?" "What did you do?" queried Valsalva. "Just what you said," replied the patient. "Just starved and stayed in bed." The aneurysm had subsided, and it no longer pulsated in the neck.

In the nineteenth century the surgical approach to the treatment of aneurysm of the innominate artery first began to attract attention. In 1829 Valentine Mott,⁷ of New York, following the suggestion of Mr James Wardrop,⁸ surgeon to the king of England, was the first American surgeon to ligate the right carotid artery in a case of innominate aneurysm.

Such a procedure must have been extremely difficult and hazardous before the days of ether, yet additional cases soon were reported, after the introduction of ether a considerable literature on the surgical treatment of innominate aneurysm developed.

Certain striking cases have been reported. Barwell,⁹ in 1877, ligated the right common carotid and right subclavian arteries of a 45 year old laborer, a patient at the Charing Cross Hospital, London, who had an aneurysm at the right of the base of the neck, reaching as far as the cricoid cartilage. Seven weeks after the operation the visible enlargement had decreased and was reduced to about the size of a pigeon's egg, being located behind the right sternoclavicular joint. Autopsy finally verified the presence of a small innominate aneurysm which had

6 Matas, R. On the Treatment of Aortic Aneurysm by the Method of Jugulo-Carotid Anastomosis. A Discussion, New Orleans M & S J 84 448 (Dec) 1931

7 Mott, V. Aneurysm of the Arteria Innominata, Involving the Subclavian and the Root of the Carotid, Successfully Treated by Tying the Carotid Artery, Am J M Sc 5 297 (Feb) 1829

8 Wardrop, J. On Aneurysm and Its Cure by a New Operation, London, Longman & Co, 1828

9 Barwell, R. On Aneurysm, Especially of the Thorax and Root of Neck, London, Macmillan & Co, 1880, pp 32-77

shrunk and was sclerosed. In this country Mynter,¹⁰ in 1887, and Gay,¹¹ in 1897, both performed successful ligations. In 1909 Schwyzer¹² performed distal ligation of the right common carotid and right subclavian arteries for an innominate aneurysm presenting in the neck. The patient lived at least twenty-two years after the ligation. In this case the tumor also disappeared. A patient with a perforating aneurysm was operated on by Rosenstern¹³ and was said to have lived many years. Another case that was remarkable for the long duration of the condition was mentioned by Miller,¹⁴ of London. His patient had an aneurysm of the innominate artery which presented at the base of the neck when he was 41 years old. The aneurysm was treated by injections of quinine hydrochloride and ethyl carbamate and also by ligation of the right common carotid and subclavian arteries when the patient was aged 56. He died at the age of 64 as a result of internal rupture of the aneurysm. In 1929 James Greenough¹⁵ gathered together the literature on operations on the innominate artery. He stated as his belief from the cases reported and his own experience that if the operation is for aneurysm, distal as well as proximal ligation should be done and the sac should be extirpated or destroyed. While among all the 91 reported cases which he collected the mortality after ligation was 56 per cent, when the cases were grouped chronologically it was clear that as surgical methods had improved the operative mortality of this type of operation had diminished. His conclusion was that operation is justifiable and if contemplated should be done early.

The following report is of a case which I had the opportunity of studying.

CASE 1—The patient was a 64 year old Irishman. Recently he had worked as a day laborer, though in the early days he had been a sailor, roving pretty much all over the world. He entered the hospital on Jan 15, 1937, complaining of a sizable lump in his neck and of pain in his right shoulder.

When he was 18 years old he had a chancre, which was treated for two years with medicine administered in pill form. This was the only treatment for syphilis that he had received. Eleven years before entry to the hospital he first noticed "neuritis" of the right shoulder. This consisted of a sharp shooting pain which

10 Mynter, H. Aneurysm of Innominate Artery Treated with Ligation of Right Carotid and Subclavian Arteries, *M. Rec.* **32** 507, 1887.

11 Gay, G. A Case of Ligature of Innominate Artery for Aneurysm, *Boston M. & S. J.* **137** 13, 1897.

12 Schwyzer, A. Aneurysm of the Innominate Artery, *Ann. Surg.* **96** 666 (Oct.) 1932.

13 Rosenstern, cited by Osler, W. *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, chap. 22, p. 888.

14 Miller, C., Dolbey, R., and Ballance, C. Aneurysm of the Innominate Artery. A Twenty-Three Years' History, *Lancet* **1** 778 (April 14) 1934.

15 Greenough, J. Operations on the Innominate Artery. Report of a Successful Ligation, *Arch. Surg.* **19** 1484 (Dec.) 1929.

radiated down his arm For two years he suffered from this and by way of treatment took some pills, though what they contained he did not know eventually however, the pain disappeared

For the past nine years he had felt fairly well Then about eight weeks before he entered the hospital, the pain in the shoulder returned Along with it he noticed the appearance of a small nontender pulsating lump on the right side of his neck just above the clavicle This grew rather rapidly at first but more slowly in the few weeks before his entry, finally attaining the size of an orange He did not complain of any symptoms from compression, such as dysphagia or dyspnea, however, he did have a slight hacking cough

For two weeks before entering the hospital he suffered from what he described as a boring pain between the shoulders This was relieved when he sat up and also by strenuous exercise, such as chopping wood

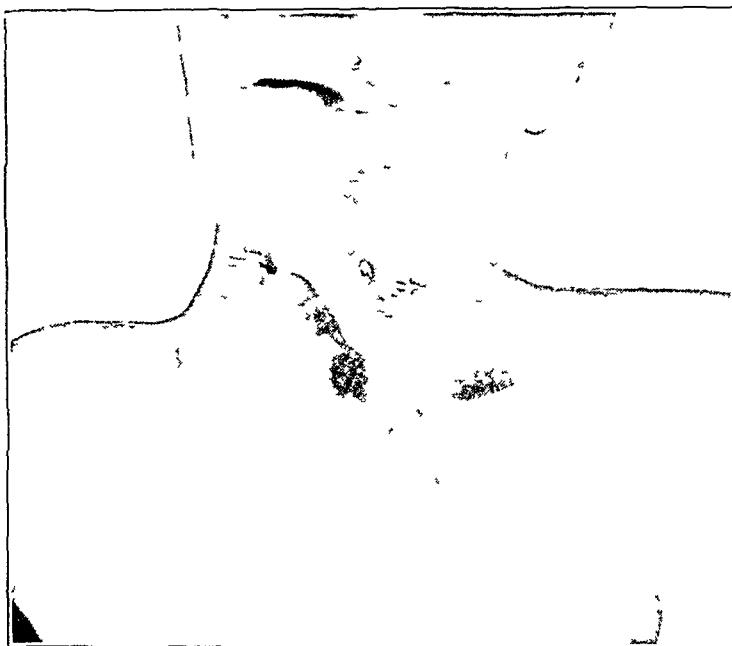


Fig 1 (case 1)—Aneurysm of the innominate artery The inner half of the right clavicle is obscured The thyroid cartilage and the trachea are displaced to the left The prominent bulging just below the thyroid cartilage was the site of greatest pulsation and later became the site of rupture

On physical examination he was observed to be well developed and robust, presenting a large pulsating lobulated mass in the right side of his neck It measured 8 cm in diameter at the base and projected outward for a distance of 4 cm Its outer lateral portion was firm, as compared to the inner portion near the midline, where it was thin walled The right sternoclavicular joint was displaced anteriorly The skin over the mass was bluish and purplish and was darker than the surrounding skin The trachea was markedly displaced to the left, and the right sternomastoid muscle was pushed to the right by the tumor Visible pulsation also was seen in the left lower portion of the back in the ninth and tenth intercostal spaces, where there was considerable retraction of the thoracic wall as well

The heart sounds were heard in the mass, but there was no bruit There was tenderness over the right sternoclavicular joint The apex impulse of the heart was seen and felt within the midclavicular line There was no increase in retrosternal dullness, nor was there increased dullness in the second or third right inter-

costal spaces. The sounds were regular and of good quality. A soft blowing systolic murmur was heard in the second right intercostal space, but no diastolic murmur was heard. The second aortic sound was not accentuated.

There was a slight amount of peripheral sclerosis. The blood pressure in the two arms was the same. The pulse volume was thought to be less in the right arm than it was in the left. The venous pressure was 80 mm of water in the right arm and 95 mm of water in the left. No rales were heard in the lungs, though on both sides of the upper portion of the chest the breath sounds were suppressed. The voice was normal, and there was no laryngeal paralysis. The right pupil was slightly larger than the left.

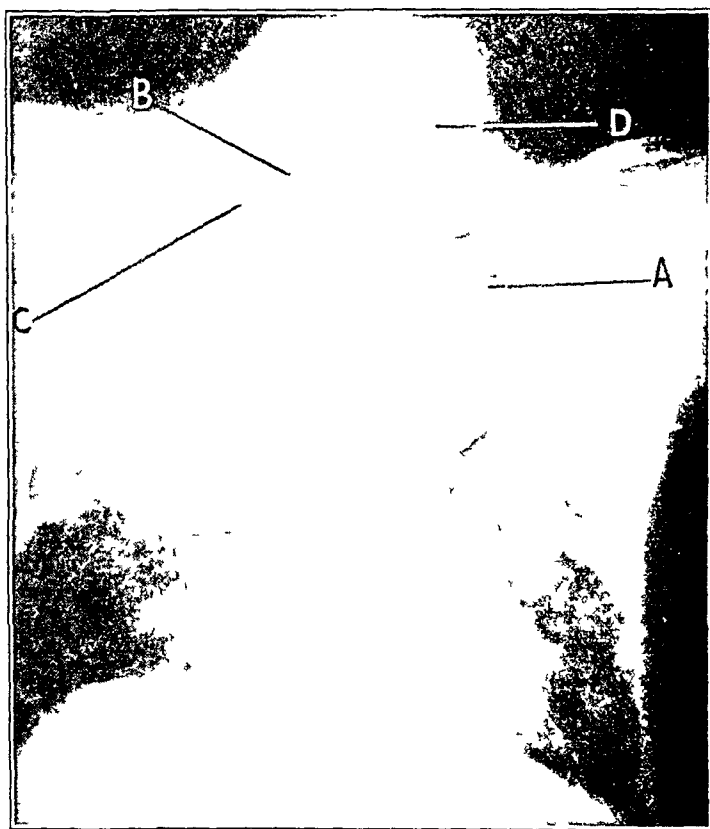


Fig 2 (case 1)—Roentgenogram showing (A) the sacculated aneurysm of the descending portion of the aorta just beyond the arch, with calcified plaques in the wall of the sac seen in the third left intercostal space, (B) the aneurysm of the innominate artery, (C) erosion of the sternal end of the right clavicle, and (D) deviation of the trachea.

It is worth reemphasizing that there were no symptoms of compression, in spite of the fact that the trachea and the larynx were so markedly displaced.

The urine and blood were normal. The Wassermann reaction was positive. Numerous electrocardiographic tracings at times showed many extrasystoles of auricular and ventricular origin, though no other abnormality in rhythm was ever noted, the ventricular complex was abnormally slurred and notched, suggesting an impaired myocardial function.

Roentgenologic and fluoroscopic examinations of the chest revealed a dilated aortic arch with an aneurysm of the descending portion of the aorta and an aneurysm of the innominate artery. The heart was but slightly enlarged. There

were displacement of the trachea to the left, erosion of the upper border of the first rib, erosion and displacement of the sternal end of the right clavicle and erosion of the right borders of the second, third and fourth thoracic vertebrae.

By way of treatment the patient was put to bed. At first he complained bitterly of pain in the right shoulder joint and was given opiates for relief. On the third day of hospitalization his temperature became slightly elevated, there was leukocytosis and the pain was increased. This febrile episode lasted for four days, it was thought that he might have had a small rupture in one of the aneurysms. Antisyphilitic treatment was administered in the form of bismuth subsalicylate and potassium iodide and eventually small doses of neoarsphenamine. Under this therapy his condition definitely improved, he was able to sit up, shave himself and walk about without discomfort. During this period of observation, however, the tumor in his neck appeared to increase in size rather than to diminish.

He grew to feel so well that he was discharged in comparatively good condition after seventy-three days of hospitalization. A few days later, however, he walked a distance of approximately five miles, and shortly afterward there devel-

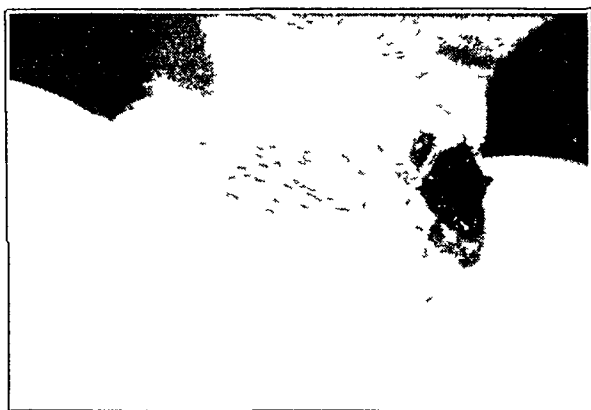


Fig 3 (case 1)—Rupture of the aneurysm of the innominate artery. Osler said in regard to similar cases: "Reddening of the skin occurs with edema. A spot of necrosis forms which increases in size slowly. The aneurysm first 'weeps' and finally bursts with fatal hemorrhage." In this case the spot of necrosis grew to form an ulcer, 3 cm in diameter, before the final rupture.

oped what he thought was a severe cold with a cough. The mass in his neck became painful, and the overlying skin became reddish. On one of the prominent lobulations near the midline there appeared a discolored area which looked like beginning ulceration. He became anxious over the changes which had taken place in the tumor and therefore returned to the hospital.

The physical findings were unchanged except that the mass in the neck pulsed more violently than before and the skin over it was cyanotic and edematous. It was a case of this type that Sir William Osler¹ must have had in mind when he described the events that take place in external perforation of an aneurysm: "Reddening of the skin then occurs with edema. A spot of necrosis forms which increases in size slowly. The aneurysm first 'weeps' and finally bursts with fatal hemorrhage." This is precisely what happened in the present case in the course of the next few days.

The necropsy confirmed the clinical findings. There were a large saccular aneurysm of the innominate artery with perforation, a fusiform dilatation of the arch of the aorta, resulting from old syphilitic aortitis, and an aneurysm of the

descending aorta which extended to the midthorax. The innominate aneurysm measured 10 cm in length and 7.5 cm in diameter. It was filled with soft, dark crimson clot. It had eroded through the sternal end of the right clavicle and the right borders of the second, third and fourth thoracic vertebrae, it had flattened the right lobe of the thyroid gland and it had displaced the trachea, without, however, obstructing either it or the esophagus. Death, of course, occurred from external rupture, with almost immediate exsanguination.

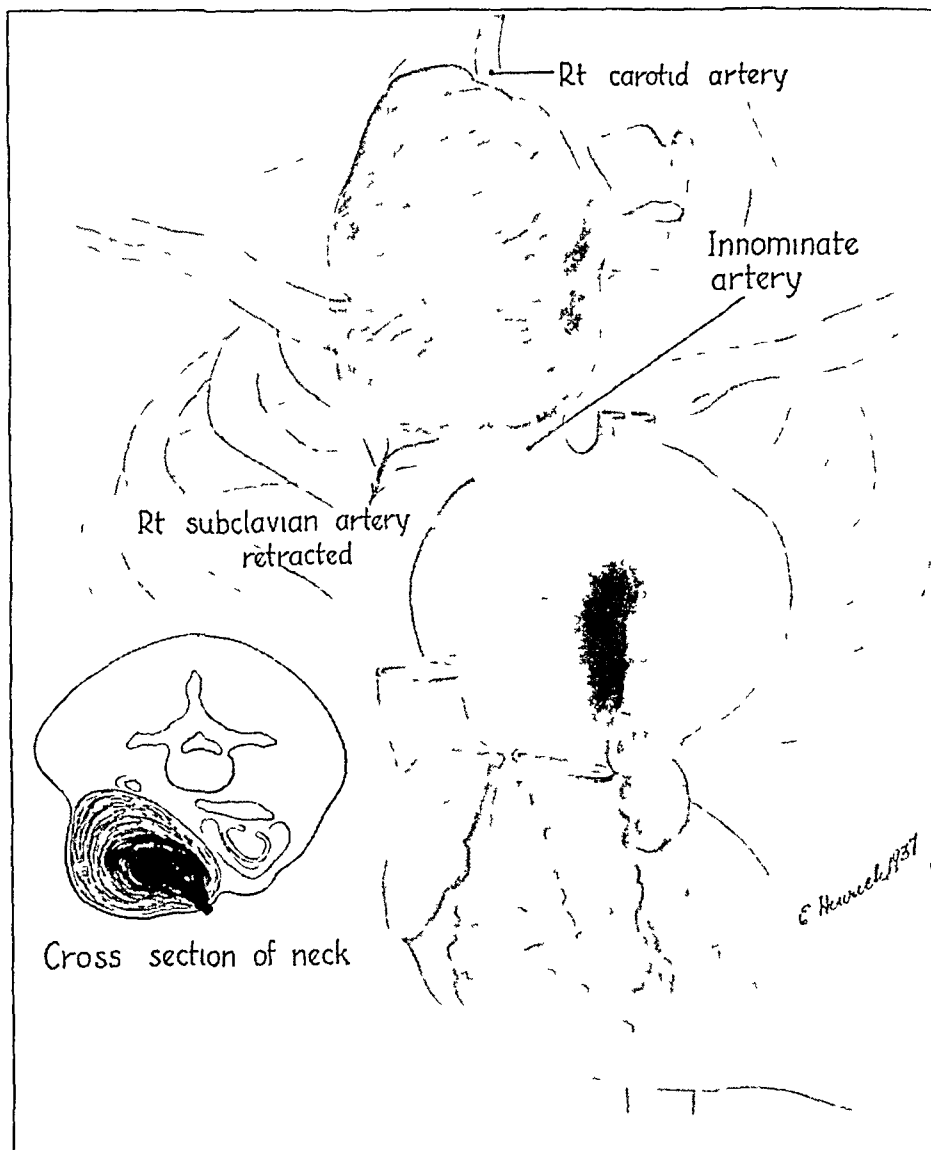


Fig 4 (case 1) —Showing the relation of the aneurysms to the thoracic cage and the structures in the neck

This was the first case of aneurysm that I had seen in which rupture occurred. It made an unforgettable impression, particularly as there still is uncertainty in my mind as to whether surgical treatment combined with antisyphilitic treatment was not indicated and might not have produced a more satisfactory therapeutic result than did medical treatment alone.

Obviously a great deal is known of innominate aneurysm. Its topographic anatomy has been abundantly described. Its symptoms also are well recognized. Usually the earliest symptom is pain in the right shoulder. A pulsating tumor in the neck soon is likely to appear. The tumor spreads along the line of least resistance, and this characteristically is upward under the sternomastoid muscle into the neck or, more rarely, downward into the mediastinum or pleural cavity, displacing the heart to the left. Curiously, although the aneurysm advances and erodes, compresses and displaces, it is less likely to cause symptoms from pressure on structures like the larynx and trachea than is an aneurysm arising in the aorta. This usually is regarded as an important differential point, an aneurysm of the arch of the aorta is notorious for giving early signs of compression because of the narrow space between the posterior surface of the sternum and the bodies of the vertebrae. An



Fig 5—Figures from the case report by Richard Barwell (1877). The right common carotid and subclavian arteries were ligated. The patient lived a few months after operation and died of bronchopneumonia following exposure. Necropsy showed a small innominate aneurysm that was shrunken and sclerosed.

innominate aneurysm, in contrast, has more room in which to grow. If present in the neck, it is likely to be high, while an aneurysm of the arch will not extend much above the clavicular line. Finally, roentgenography and fluoroscopy should make it possible to recognize a thoracic aneurysm easily and to determine the point of origin with great accuracy.

That any internal aneurysm is essentially a hopeless affliction is certain. An innominate aneurysm, like any other aneurysm, is likely to rupture—not often externally but frequently into the trachea, bronchus, esophagus, mediastinum or pericardial or pleural cavity. Rupture is the common cause of death.

In recent years the medical treatment of thoracic aneurysm has received all the emphasis, the modern textbook of medicine failing to

emphasize the essential anatomic difference between aneurysm of the aorta and aneurysm of the vessels at the base of the neck and the fact that their therapy may differ. One must go back to Osler to be told that the differential diagnosis of aneurysm presenting in the neck is important because such an aneurysm is amenable to surgical procedures while one near the base of the heart is not.

No doubt the improving therapy of syphilis has much to do with modern indifference to aneurysms. In the first place, aneurysms now are comparatively rare and are likely to become even rarer as syphilis is recognized more easily and treated more adequately. In the second place even the medical treatment of aneurysm is vastly better than it was, for example, when Osler wrote the first draft of his textbook. Now, as Moore, Dangle and Reisinger¹⁶ have reported, prompt symptomatic relief, especially relief of paroxysmal and exertional dyspnea and of pain, is likely to be obtained in the medical treatment of aneurysm, and life is prolonged. Nevertheless, in spite of such advances in medical treatment, I believe that Osler's opinion should still be maintained. The differential diagnosis of aneurysm presenting in the neck still is important because such an aneurysm is amenable to surgical procedures while one near the base of the heart is not. If one could duplicate Barwell's⁹ case, Schwyzer's¹² case (in which the patient lived for more than twenty-five years after ligation) or Miller's¹⁴ case (in which the patient lived for twenty-three years after ligation), one would feel well satisfied.

As has been mentioned, the surgical procedures which have been advocated for the treatment of innominate aneurysm include ligation of the right common carotid artery and the right subclavian artery, ligation of the innominate artery and vein as well, wiring and the causation of clot formation by electricity within the aneurysmal sac, as suggested by Reid,¹⁷ injection of quinine hydrochloride and ethyl carbamate, as suggested by Miller¹⁴ for the same purpose, and even production of an arteriovenous fistula between the common carotid artery and the internal jugular vein, as suggested by Babcock¹⁸ and McCarthy¹⁹.

16 Moore, J. E., Dangle, J. H., and Reisinger, J. C. Treatment of Cardiovascular Syphilis. Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, *Arch Int Med* **49** 879 (June) 1932.

17 Reid, R. M. Aneurysms in the Johns Hopkins Hospital. All Cases Treated in the Surgical Service from the Opening of the Hospital to January 1922, *Arch Surg* **12** 62 (Jan.) 1926. Reid and Andrus.²

18 Babcock, W. W. Newer Surgical Methods of Treating Diseases of the Vascular System, *Am J Surg* **16** 401 (June) 1932.

19 McCarthy, P. A. Treatment of Aneurysms of the Thoracic Aorta and Innominate Artery by Distal Arteriovenous Anastomosis. Observations of Ten Cases with Operations in Eight Cases, *Ann Surg* **91** 161 (Feb.) 1930.

No doubt technical difficulties in the way of these operations may be great. On the other hand, the skill of the modern surgeon is uncanny. In reconsidering the case which has just been described, it might have been possible, in the light of the necropsy observations, for a dextrous surgeon to have tied the subclavian and carotid arteries without rupturing the aneurysm, and this might have been a more beneficial form of treatment than the one employed. I believe that the same argument can be applied to the following case of a patient of Dr. Joseph Pratt and Dr. Samuel Proger at the Boston Dispensary, the record of which they have allowed me to study and to include in this paper.

CASE 2—A 48 year old Scotchman, a seedsman, was admitted to the diagnostic ward of the Boston Dispensary on July 25, 1932. He complained of a lump in

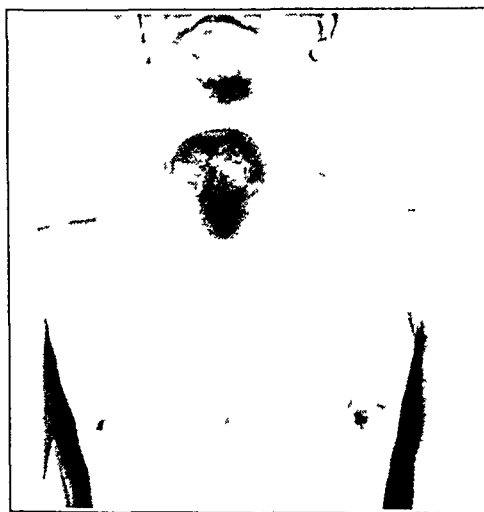


Fig. 6 (case 2)—A large innominate aneurysm presented at the base of the neck, with an area of necrosis in its most prominent part, at which point the final rupture took place. (Reproduced with the permission of Dr. Pratt and Dr. Proger of the Boston Dispensary.)

his neck. When he was 18 he had a penile sore followed by a rash. This was untreated, though in 1927 he received six injections of arsphenamine for "recurring sore throat."

He had been well all his life until about two months before he entered the hospital. Then he noticed the appearance of a small tumor on the lower right side of his neck. This grew rapidly, it pulsated, it was not painful and it caused no symptoms of pressure.

Physical examination revealed just above and to the right of the suprasternal notch, an oval pulsating mass, 5 by 4 by 2.5 cm., over which the skin was tense and reddened. The sternomastoid muscle was displaced by the tumor. The retrosternal dulness was increased. The heart was not enlarged. No murmurs were heard. The lungs were normal. The blood and urine were normal. While the Wassermann reaction was negative, both the Kahn and the Hinton test gave a positive reaction. Roentgenologic and fluoroscopic examination of the chest showed a large expansile mass in the right upper portion of the mediastinum apparently

continuous with the ascending aorta but extending upward and forward in the neck. The tumor had eroded the manubrium and the sternal end of the right clavicle, and it had displaced the trachea slightly to the left. Five months later the tumor had increased greatly in size, and the skin over it was necrotic. Presently this area of necrosis increased slowly, the aneurysm began to weep and eventually it burst, with fatal hemorrhage.

While necropsy was not performed a comparison of the findings in this case with the findings in the former case makes it seem highly

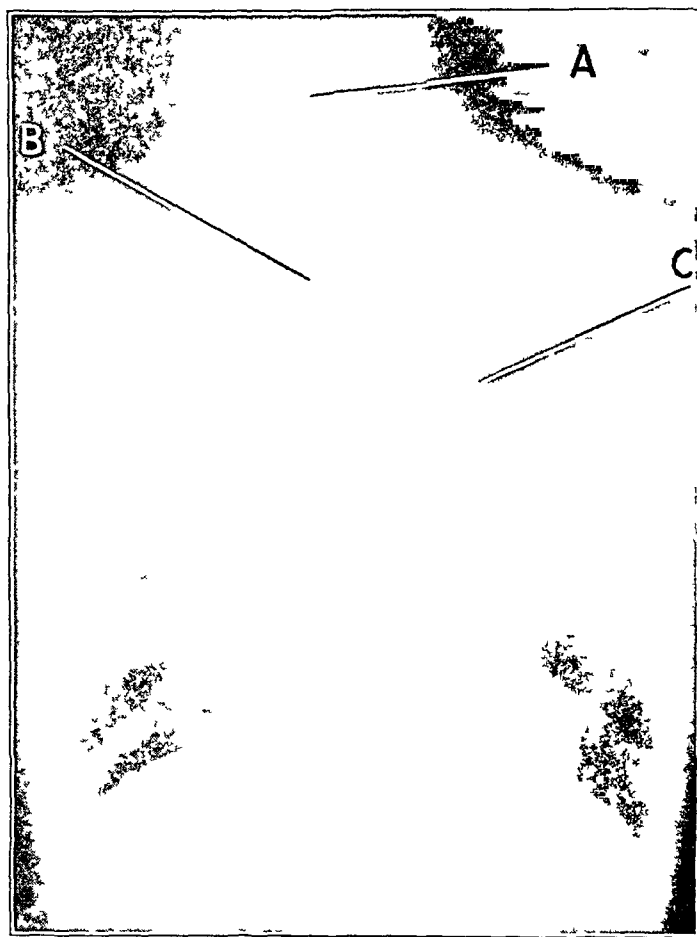


Fig 7 (case 2)—Roentgenogram showing (A) the superior border of the aneurysm presenting in the neck, (B) the sacculated innominate aneurysm continuous with the ascending aorta and extending up into the neck and (C) the arch of the aorta displaced to the left. This was not an aneurysm of the aorta, as verified by fluoroscopy. The trachea cannot be seen in this roentgenogram on account of the density of the mass, but by fluoroscopy it was shown to be displaced to the left. (Reproduced with the permission of Dr Pratt and Dr Proger, of the Boston Dispensary.)

probable that here too was an innominate aneurysm with rupture. Probably it would scarcely have been feasible to tie the innominate artery in this case, but possibly ligation of the subclavian and carotid arteries might have been accomplished with good effect.

In certain cases technical difficulties brought up by the complicated anatomic relations of an innominate aneurysm may make the surgical treatment of the tumor almost impossible

CASE 3—An American painter 65 years old was admitted to the Massachusetts Memorial Hospitals on Dec 13, 1930. He denied having had syphilis, though the Kahn and Hinton tests gave positive reactions. About ten years before entrance he first began to have palpitation of the heart and frequent spells of coughing. About a year before entry he was forced to give up work because, in addition to persistent dyspnea and orthopnea, he had edema of the legs.

There was no visible or palpable tumor of the neck. The heart was enlarged on percussion. No murmurs were heard. A roentgenogram of the chest showed a large dense shadow at the apex of the right lung and in the anterior mediastinum, due apparently to a mass, which appeared to displace the heart downward and to the left and which also displaced the trachea to the left. The patient died of congestive heart failure. Necropsy revealed an aortic aneurysm involving the innominate and right subclavian arteries as well as the arch of the aorta.

In this case, in which the innominate aneurysm had grown downward rather than upward, in which the aneurysm was practically inseparable from the arch of the aorta and in which it also involved the right subclavian artery, any successful operative procedure would have been almost unthinkable.

These 3 cases make a large enough group from which to draw certain generalizations concerning aneurysm of the innominate artery with which to awaken interest in an unusual medical disorder which has apparently been neglected of late by clinicians. Aneurysm of the innominate artery is rare, but its recognition is important. It differs from an aneurysm of the aorta by being more amenable to surgical treatment. An innominate aneurysm has a fairly definite clinical course and a clinical picture which make diagnosis possible in the majority of instances, especially when roentgenograms and fluoroscopy are available as diagnostic aids. The presence of a pulsating tumor above the episternal notch should make one suspicious of an aneurysm of the innominate artery which is presenting in the neck. The most satisfactory treatment of aneurysm of the aorta consists in the long-continued, intelligently administered treatment of syphilis. Treatment of aneurysm of the innominate artery not only should include treatment of the syphilis but also should be regarded as having surgical implications. The surgical attack should be undertaken early, before the aneurysm becomes large, as it should be borne in mind that the aneurysm may grow rapidly in the course of several weeks. It may be that the combination of anti-syphilitic and of surgical treatment will accomplish in selected cases a more perfect therapeutic result for this type of aneurysm than has been hitherto generally obtained.

DARK ADAPTATION OF THE EYE AND VITAMIN A STORAGE IN YOUNG ADULTS

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AND

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Evidence for the belief that night blindness represents the first symptom of vitamin A deficiency has been accumulating for some time

Until recently the condition of night blindness has been considered rare in North America Hess and Kirby,¹ seeking to determine the incidence of the condition, sent questionnaires to American ophthalmologists inquiring as to the number of cases that they had identified among their patients, and all who reported stated that night blindness is uncommon This was interpreted to mean that deficiency of vitamin A is of infrequent occurrence in North America

The later work of Jeans and Zentmire² with the Buch-Hirschfeld visual photometer and that of Jeans Blanchard and Zentmire³ with the biophotometer indicated that night blindness is common among children These workers also presented evidence of vitamin A deficiency as a causative factor Likewise the study of Park⁴ and of Jegheis,⁵

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A preliminary report, an abstract of which appeared in the *Journal of Home Economics* for October 1937, was presented before the division on food and nutrition at the thirtieth annual meeting of the American Home Economics Association at Kansas City, Kan, on June 22 1937

1 Hess and Kirby, cited by Eddy, W H, and Dalldorf, D The Vitamins, Baltimore, Williams & Wilkins Company, 1937

2 Jeans, P C, and Zentmire, Z A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J A M A* **102** 892-895 (March 24) 1934, The Prevalence of Vitamin A Deficiency Among Iowa School Children, *ibid* **106** 996-997 (March 21) 1936

3 Jeans, P C, Blanchard, E, and Zentmire, Z Dark Adaptation and Vitamin A A New Photometric Technic, *J A M A* **108** 451-458 (Feb 6) 1937

4 Park, I O Preliminary Observations of Vitamin A Deficiency as Shown by Studies with the Visual Photometer, *J Oklahoma M A* **28** 359-364 (Oct) 1935

5 Jegheis, H Night Blindness as a Criterion of Vitamin A Deficiency Review of the Literature, with Preliminary Observations of the Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, *Ann Int Med* **10** 1304-1334 (March) 1937

using the Buch-Hirschfeld photometer, pointed to the frequent occurrence of night blindness and of moderate vitamin A deficiency among adults

The purpose of our study was (1) to obtain data to use in setting up standards for normal biophotometric readings for young women, (2) to determine the extent to which poor dark adaptation occurs in young college women and (3) to seek further evidence for the relation between vitamin A deficiency and subnormal dark adaptation, as measured with the biophotometer

At the time that this study was made there were no reports of biophotometric tests on adults. There has since been published the work of Jegheis⁶ with freshman medical students, chiefly men, employing this newer photometric technic. The author reported relatively poor dark adaptation in 35 per cent of the subjects tested

METHOD

The subjects for our study were freshman women ranging in age from 17 to 22 years. As a matter of convenience they were chosen from the students attending the freshman classes on foods at Purdue University, with no attempt at special selection.

Each subject was asked to keep a record of her diet for one week, with the thought that such a record might serve as an indication of the dietary habits of the subject and might possibly account for any marked individual variation in vitamin A storage. In order to secure as accurate and detailed a record as possible, each subject was asked to keep slips recording the number and size of servings (small, medium or large) of each food eaten. Between-meal "snacks" were also included. Daily summaries were made from these slips on special forms prepared for the purpose. From these forms weekly dietary summaries were made so as to permit comparison of the diets of the different subjects.

Approximately half the total group were living at the Women's Residence Hall, their period of residence having covered about four months. The other half secured meals from a variety of eating places on and off the campus.

The testing technic was essentially that of Jeans, Blanchard and Zentmire³. In order to insure the carrying out of all the tests in a uniform manner, detailed directions for each step of the procedure, including instructions to the subject, were formulated, and these directions were carefully followed.

Single tests were made for 94 students. Those showing relatively poor dark adaptation were tested again in a few days, and if confirmation of the first test was obtained, they were selected for further study. In a few instances a third test was made, with the result that there were some eliminations and a final selection of 16 subjects to serve as an experimental group. To this group were added 2 subjects whose biophotometric tests indicated good dark adaptation. The subjects were paired on the basis of the biophotometric readings, the readings in most instances showing little divergence for the members of a pair. One member of each pair served as a control and the other received, in addition to the regular

6 Jegheis, H. The Degree and Prevalence of Vitamin A Deficiency in Adults, with a Note on Its Experimental Production in Human Beings, *J. A. M. A.* 109 756-761 (Sept. 4) 1937.

diet, three halibut liver oil capsules daily, representing 28,000 to 29,000 U S P units of vitamin A ⁷ Tests were repeated at weekly intervals on the controls and on those receiving halibut liver oil, the members of a pair being tested on the same day of each week. The experiment was continued for five weeks.

RESULTS

An arbitrary grouping of the initial readings for recovery after exposure to the bright light for the original 94 biophotometric tests and the distribution of the subjects over the range of readings obtained are recorded in table 1.

An appraisal of the results in terms of normal is difficult to make as work with the biophotometer, particularly with adult subjects, is too limited as yet to furnish anything definite in the way of standards. In this study the subjects having a light requirement greater than 1.5 milli-foot-candles immediately after exposure to the bright light were definitely considered to have poor dark adaptation. It was from this group that 16 of the experimental subjects were chosen. Second and

TABLE 1—*Results of Biophotometric Tests*

Initial Recovery Reading, Milli Foot Candles of Light	Number of Subjects	Per Cent of Total
Less than 0.5	10	10.6
0.5 to 1	33	35.1
1 to 1.5	26	27.7
Greater than 1.5	25	26.6

third tests, however, gave readings that placed some of them in the group immediately above, with the readings for 3 of the subjects falling slightly below the lower range for that group. The 2 experimental subjects representing good dark adaptation were selected from the first two groups, with readings of 0.38 and 0.52 milli-foot-candle, respectively.

Attention is centered on the first reading of the recovery period after exposure to the bright light, because it appears to be the most significant one. Jeans, Blanchard and Zentmire, however, while emphasizing the importance of this reading have regarded the entire period of recovery as having significance. They have stated that those with normal dark adaptation have final readings of less than 0.05 milli-foot-candle except in cases in which the "visual threshold" is increased by causes other than vitamin A deficiency. In the present study 3 of the 5 subjects whose final readings were 0.05 milli-foot-candle or greater were in the group showing the most deficiency (initial readings for the period of recovery greater than 1.5 milli-foot-candles). One was in the group with readings of 1 to 1.5 milli-foot-candles, and the other showed readings close to the upper limit of the range 0.5 to 1 milli-foot-candle.

⁷ The capsules, with assay figures, were supplied through the Wm. S. Merrell Co., Cincinnati.

The results of the analysis of the dietary records are shown in table 2. An examination of this table reveals nothing that would account for marked variations in the vitamin A intake of the subjects, so that the differences in vitamin A storage which the biophotometric readings seem to indicate cannot be explained on the basis of the eating habits of the subjects at the time that the tests were made. A question might be raised, however, as to how far such records may be relied on to give a true picture of even the qualitative aspects of the diet.

TABLE 2—*Analysis of the Dietary Records Showing the Average Servings per Person per Day*

Group*	Fruits										Bread	Cereals Other Than	Meat, Fish, Poul try	Eggs, Cheese	Cof fee, Coca Cola, Mal ted Milk	Cake, Pas try, Sweets
	Vegetables					To										
	Milk	Green	Yel low	Pota toes	Other	Oran ges	Grape fruit	ma- toes	Other							
A	1 31	0 93	0 29	0 77	0 53	0 22	0 30	0 27	1 55	2 90	0 37	1 42	0 51	1 72	1 34	
B	1 04	1 00	0 26	0 76	0 50	0 18	0 28	0 28	1 83	2 80	0 24	1 45	0 40	1 07	1 45	
C	1 34	0 98	0 28	0 62	0 76	0 16	0 51	0 35	1 80	2 98	0 17	1 48	0 52	0 84	1 12	

* Group A represents the total group, group B includes 16 subjects with good dark adaptation and group C includes 16 subjects with poor dark adaptation. Two subjects in group B had been taking cod liver oil or vitamin A concentrates.

TABLE 3—*Initial Recovery Readings in Milli-foot-Candles*

Subjects Receiving Halibut Liver Oil							Controls						
Sub ject No	Orig inal Test	Week of Experiment					Sub ject No	Orig inal Test	Week of Experiment				
		1st	2nd	3rd	4th	5th			1st	2nd	3rd	4th	5th
7	0.72	0.76	0.58	0.29	0.58	0.38	81	0.63	0.69	1.00	0.84	0.92	0.84
11	1.95	1.48	1.00	0.44	0.84	0.76	73	1.95	1.80	1.48	1.60	1.80	1.80
84	1.48	0.63	0.76	0.76	1.00	1.10	2	1.48	1.36	1.36	1.36	1.80	1.80
52	1.36	1.00	0.315	0.69	0.52	0.44	70	1.22	1.10	0.63	0.76	0.69	0.63
27	1.48	1.00	0.52	0.58	0.69	0.69	76	1.22	1.36	1.00	1.22	1.00	1.36
32	1.22	1.36	0.36	1.10	1.00	1.00	36	0.92	1.48	1.22	0.92	1.36	1.10
60	1.95	1.36	1.00	1.36	0.63	0.84	71	1.00	0.84	1.22	1.60	1.80	1.10
88	2.16	1.95	1.36	1.48	0.76	0.92	46	1.48	1.80	2.40	0.69	2.40	1.36
90*	0.52	0.24	0.29	0.18	0.16	0.195	59*	0.38	0.44	0.47	0.63	0.63	0.69

* Subjects 59 and 90 are the two whose original readings placed them in the group considered to have good dark adaptation.

In table 3 are recorded the weekly initial readings made during recovery for the subjects receiving halibut liver oil and for their respective controls over a period of five weeks. It will be noted that there were fluctuations back and forth in both groups, but definite improvement in the subjects to whom the halibut liver oil capsules were administered was evidenced by the decreased requirements of light of the latter after the first or second week in contrast to that of the controls, for whom subsequent readings were in most cases as high as or higher than those obtained at the beginning. The improvement in the subjects who originally showed a high requirement of light is in accord with the findings of other workers. But the results obtained with the pair con-

sidered to have good dark adaptation seem to point to something that has not previously been noted, that is, the possibility that even very low readings may not indicate optimal storage of vitamin A. This point is now under further investigation.

There was rather wide variation in the minimal biophotometric readings obtained for the different subjects receiving halibut liver oil. The time required to reach this stage also varied, the range being from one to four weeks, with no consistent relation between the original readings and the time period. There were few instances in which there was improvement after four weeks.

These observations seem to suggest that there are individual variations with regard to what constitutes the best dark adaptation obtainable. It also appears that the intake of vitamin A necessary for optimal storage varies with different subjects, assuming that optimal storage for a given subject has been obtained when no further improvement results with a continued high intake of vitamin A. A better interpretation of the results observed may be that they indicate a varying ability to utilize and store the ingested vitamin A, particularly as it affects the rate of regeneration of the visual purple.

SUMMARY AND CONCLUSIONS

Single biophotometric tests of a group of 94 college freshman women gave readings that were interpreted to indicate poor dark adaptation in at least 26.6 per cent of the cases.

The daily administration of 28,000 to 29,000 U. S. P. units of vitamin A in the form of halibut liver oil capsules to half the 18 experimental subjects resulted in lowered readings in contrast to those for the respective controls, which were in most instances as high as or higher at the end of the five week experimental period than at the beginning. This improvement in the subjects receiving halibut liver oil and the failure of the corresponding controls to improve was evident not only in the eight pairs of subjects whose original tests were thought to indicate poor dark adaptation but also in the pair who at the beginning of the experiment appeared to have good dark adaptation. The improvement, however, did not always proceed regularly, there was some fluctuation back and forth both for the subjects receiving halibut liver oil and for the controls.

Minimal biophotometric readings, as well as the time required to reach this stage, varied with the different subjects to whom the halibut liver oil was administered.

The pair with good dark adaptation gave lower original readings than were ever attained by most of the more deficient subjects, yet the member of this pair to whom halibut liver oil was administered proved to be capable of further improvement.

The improvement resulting from the administration of halibut liver oil to the more deficient subjects agrees with the findings of other workers and gives increased evidence for the alleged relation between vitamin A deficiency and subnormal dark adaptation, as measured with the biophotometer.

The study also furnishes meager evidence for the view that even low readings may not indicate optimal vitamin A storage. There is need for further investigation on this point.

In general, it may be concluded that there is a variation in what constitutes the best dark adaptation obtainable for a given person. It appears that there are differences in the ability to utilize and store the vitamin A ingested beyond a certain point, particularly as it affects the rate of regeneration of the visual purple in adapting the eye to dim illumination.

BILATERAL SPOROTRICHOSIS OF THE BREAST

REPORT OF A CASE

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AND

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A careful though not complete survey of the literature covering sporotrichosis fails to reveal any reports of cases of invasion of the female breast by *Sporothrix*. We are recording the present case because of its unusual diagnostic features and because of the complete laboratory confirmation of the tentative diagnosis. It is of note that the prompt therapeutic response likewise authenticated the diagnostic premise.

The first recorded instance of *sporothrix* infection occurred in 1896¹. The organism in this case was identified by Irwin F. Smith and was named *Sporotrichum schenckii* in honor of the clinician who first recognized the etiologic factor responsible for the ulcerated lesion on the forearm of the patient. Since the identification of this parasitic fungus, several other cases have been recognized, notably a series of 10 cases reported by Foerster in 1926².

Sporotrichosis is a chronic infection of the cutaneous and internal structures due to various forms of the spore-forming filamentous fungi of the *Sporothrix* group. The cases in human beings recorded in the literature concern primarily the cutaneous form of the disease, in which the subcutaneous tissues are affected and in which only rarely is there dissemination to deeper or visceral organs. Various clinical forms are described, as follows:

- 1 A disseminated gummatous form, in which firm nodular swellings appear which ultimately form small abscesses with ulceration and with the production of a chronic persistent discharge
- 2 The ulcerative type, which appears to be common on the hands and arms and which strongly resembles the cutaneous form of tuberculosis
- 3 The so-called extracutaneous forms, in which ulcerous areas are found in the mucous membranes, glands, lungs, periosteum, bone or muscle
- 4 An internal form, which is presumably secondary to some cutaneous form but which has the characteristics of an acute febrile illness

1 Osler, W. Principles and Practice of Medicine, ed 11, revised by Thomas McCrae, New York, D Appleton and Company, 1930, p 235

2 Foerster, H R. Sporotrichosis. An Occupational Dermatitis, J A M A. 87 1605 (Nov 13) 1926

By far the most common type is the cutaneous or localized form with secondary regional lymphangitis. The lesion may be said to be a primary sore at the site of inoculation, then in the course of a few days to several months, small painless indolent granulomas form, which may ulcerate and produce abscesses of the "cold" type. Secondary to ulceration there is the production of fistulas or sinus tracts. As a general rule the health of the patient is relatively unaffected, except in cases of the febrile internal type. Mild anemia is said to accompany the usual course of chronicity, which varies from one to three years.

Infection with the sporothrix is most common among farmers, gardeners and laborers. It has been called an occupational disease by Foeister,² who described 10 cases due to trivial wounds of the hands or arms from the thorns of barberry bushes. In the majority of reported cases a predilection for the hands, arms and lower extremities is noted, bearing out Foeister's contention. In our case it is interesting to note that the patient was probably exposed to infection while on a visit to a farm.

REPORT OF CASE

Mrs. C. M., 20 years of age, a resident in the city, presented herself to one of us (J. L. W.) with the chief complaint of "trouble with the breast." She stated that one and one-half years previously she was kicked in the left breast by an infant with whom she was playing. The trauma was trivial, and she forgot about it until about four months later, when she noted a small lump in the breast at the site of the bruise. Questioning revealed that she had been bruised while on a visit to the home of her parents in the country, where she was in the hay fields and in the garden a great deal. After the lump was noted the skin became reddened and within a few days apparently opened spontaneously, with the discharge of greenish pus which had a foul odor and was streaked with blood. A chronic discharge was then noted for several weeks, and with the use of various "home remedies" the wound apparently closed. However, within a short time several other indurated areas appeared in the breast, which were incised by a physician, and drainage continued. Approximately ten months before she was seen by one of us (J. L. W.), while there was still a draining sinus in the left breast, a lump was noted in the upper outer quadrant of the right breast. This broke and followed about the same chronic course as that of the lump in the left breast. She stated that there had not been a great deal of soreness at any time but she noted that the glands in both axillae were enlarged, although drainage had not appeared from those areas. Recently there had been some discharge of blood-streaked pus from the right nipple.

The family history was noncontributory, as was the patient's past medical history, in that there had been no serious illnesses. The marital history revealed that the patient suspected that she was approximately five months pregnant. There had been some milky discharge from both nipples. A systemic review revealed nothing of note other than a slight cough attributed to a "cold" during the past three weeks. There had been no previous pulmonary, cardiac or gastrointestinal symptoms.

Physical examination revealed a well nourished and well developed woman with a normal temperature, pulse rate and respiration. The blood pressure was 118 systolic and 76 diastolic. Examination of the head, eyes, ears, nose and throat

showed nothing remarkable. The thyroid gland was not enlarged, and there were no palpable cervical glands. Examination of the lungs and heart revealed no physical signs of a pathologic condition.

The appearance of the breast is shown in figure 1 *A*. Both breasts were enlarged, the areolas were pigmented and Montgomery's glands were prominent. In the left breast (fig 1 *B*) there was a small sinus with indurated edges above and internal to the nipple. There were two healed sinuses, one in the internal upper quadrant and the other in the lower outer portion of the areola. In the most dependent portion of the left breast there was a large area of scar tissue in a sunburst arrangement. The breast had a hard, "ropy" feeling, and the axillary glands were palpable but nontender. In the right breast internal to the nipple was an open granulomatous-edged area, approximately the size of a quarter (fig 1 *C*). From this, thick yellowish green pus exuded, and on pressure there were some bloody streaks. On palpation the condition of the breast was essentially the same.



Fig 1—*A*, the appearance of the breasts before therapy was instituted. *B*, note the "sunburst" scar at the inferior pole. To the medial side of the upper inner portion of the nipple is an open fistula with a small headed sinus mesial and superior to it. *C*, the open granulomatous lesion on the medial side of the nipple of the right breast.

as that noted in the left side, the axillary glands were likewise enlarged. A little colostrum was expressed from both nipples.

Examination of the abdomen revealed no abnormal masses, the uterus was enlarged, there was no adenopathy and the spleen was not palpable. Pelvic examination confirmed the diagnosis of pregnancy of approximately five months. Rectal examination revealed nothing remarkable. Examination of the extremities showed no clubbing, cyanosis or edema. The neurologic examination likewise showed no abnormality.

In the office a smear was made of material from the lesion in the right breast and was examined under the microscope. At this first examination the presence of rather large, ovoid, clear bodies was detected. There were no myceliums, sulfur granules or other signs of fungoid organisms. After this examination a complete

bacteriologic and laboratory examination was made by one of us (A R K M). The bacteriologic investigation consisted of microscopic and cultural studies of the purulent discharge and of tissue from the margin of the ulcer of the right breast.

Smears of the pus were stained with the Gram, Wright and Löffler methylene blue stains. In each instance the smears showed abundant pus cells with a good



Fig 2—*A*, the mycelial growth in the original broth culture, $\times 440$ *B* subculture from the broth on Sabouraud's agar

many large mononuclear endothelioid phagocytic cells. A few deeply staining, well defined oval bodies, 1 to 2 microns in diameter, were seen, and occasionally these occurred within the large mononuclear cells. No mycelial filaments could be demonstrated in these smears.

Cultures of the pus were made in nutrient dextrose broth, on blood agar and on Sabouraud's agar. None of the cultures on blood agar produced a growth

Primary cultures on Sabouraud's agar were unsatisfactory for study owing to early contamination by the penicillium and the aspergillus

Broth culture was made by plunging a cotton swab loaded with pus into the broth and leaving it in the medium continuously After four weeks of incu-

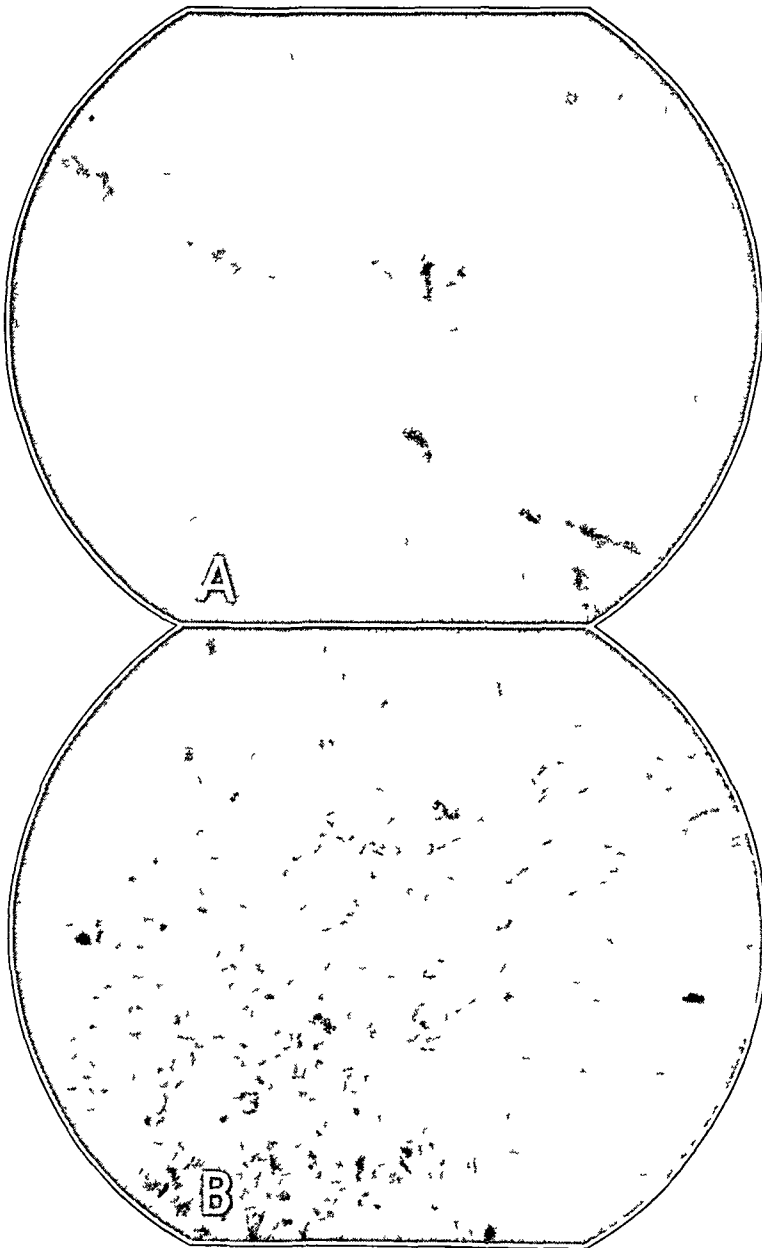


Fig 3—A, hyphae with terminal conidia from the colony shown in figure 2 B, $\times 440$ B, mycelium deep in the cutaneous tissue at the margin of the ulcer, $\times 440$

bation at room temperature a fine, fluffy white growth was seen about the cotton swab This subsequently extended up to the surface of the medium, where it formed a thick, filmy white coat Microscopic study of this growth showed a

fine, branching, septate mycelium with no sporulating asci. Some short, thickened, irregular segments were noted along various hyphae (fig 2 *A*).

This organism was transferred to Sabouraud's agar and was incubated at 37 C. It grew rapidly, producing a large, filmy white colony, which later became faintly pinkish in its central part (fig 2 *B*). Microscopically this growth showed the same fine, branching, septate mycelium. There were no asci, and conidia were seen at the ends and on the sides of the hyphae, with some tendency to grouping in whorls (fig 3 *A*).

The tissue obtained was teased out, mounted in 10 per cent solution of potassium hydroxide and examined microscopically. Granulating tissue from the base of the ulcer revealed nothing pertinent, but the deeper layers of skin at the margin of the ulcer showed fine filaments of mycelium occurring in fairly dense clusters (fig 3 *B*). No definite septations in the hyphae could be made out, but several mounts showed similar structures, and remounting in saline solution and distilled water left these structures intact. They were considered to be of fungous origin and were definitely not artefacts.

On the basis of the bacteriologic observations (the positive results of culture and the presence of mycelium in the tissue), it was apparent that we were dealing with a mycotic infection. The character of the growth obtained placed the organism in the group of fungi imperfecti, or hyphomycetes, various members of which are common causes of dermatomycoses, notably the ringworm fungi, the malassezia and the sporothrix. The arrangement of the conidia at the sides and at the ends of the hyphae is typical of the structure considered to be characteristic of *Sporothrix*, and a diagnosis of sporotrichosis was therefore deemed to be justified.

The serologic investigation consisted of Wassermann and Kahn tests of the blood. These gave negative reactions.

COMMENT

This case was interesting because of the chronicity of the condition and the apparent difficulty of making a diagnosis. Incision and drainage, presumably for abscesses, had been done on two occasions, with uniformly poor results. The general health of the patient had been unaffected. The complication of a five month pregnancy made it imperative to establish a definite diagnosis quickly in order to prepare the breasts for parturition.

Differential Diagnosis.—In the differential diagnosis we considered tuberculosis, syphilis, actinomycosis, blastomycosis, aspergillosis, other rarer types of fungous or yeast infection and lastly a streptococcic or staphylococcic infection. Tuberculosis was excluded by the normal roentgenographic appearance of the chest and the absence of other clinical signs of tuberculosis of the skin. The primary lesion of syphilis was excluded by the dark field and serologic studies. The tertiary gummatous form of syphilis likewise was excluded by the negative reactions to the Wassermann and Kahn tests and by the absence of other stigmas of either congenital or acquired syphilis. The exclusion of the various fungi and yeasts was a laboratory problem, and in this case we both found the causative organism in smears and at biopsy and were able to culture it. Streptococcic and staphylococcic infection

were ruled out by laboratory methods. Finally, as an aid in the differential diagnosis, the response to iodides was rather spectacular in this type of infection, although in certain cases of blastomycosis, therapeutic response to iodide medication is rather marked.

Clinical Course and Treatment—After the diagnosis had been definitely established, oral therapy was begun with the use of potassium iodide, starting with 0.3 cc three times a day and increasing to 2.5 cc three times a day. At first, potassium iodide³ in 1 Gm strength was administered intravenously every third day. Local application of a weak tincture of iodine was employed on the open lesion. By the end of the second week the patient had not exhibited any sign of overdosage of iodide (in these cases the patients seem to tolerate iodides exceptionally well), and the lesion in the right breast had almost completely healed. At seven months the patient was delivered of a normal healthy infant. The breasts were completely healed, but it was thought wise to give the infant a formula immediately, as further iodide therapy was necessary to prevent recurrence of symptoms in the patient. It is wise in these cases to continue treatment for at least two months after all open lesions are apparently healed.

SUMMARY

A case of bilateral invasion of the female breast by *Sporothrix* is recorded, with full laboratory confirmation and an excellent therapeutic response to iodide medication.

³ Shelmire B. Intravenous Iodine Therapy. Preliminary Report. Texas State J. Med. **22**: 644 (Feb.) 1927.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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The scope of a review of this nature is difficult to define precisely. So far as possible the object has been to include for consideration all articles which contribute new information to the subject of diseases of the blood and blood-forming organs, those which advance well thought-out speculations to explain observed phenomena and those which supplement or confirm the present beliefs. In the interests of the reader it has seemed best to correlate in connected exposition the material reviewed, although in accomplishing this it has at times been necessary to give what may seem undue weight to certain articles, while slighting others of equal merit. It is, of course, unavoidable that a number of significant communications should be passed over entirely but it is hoped that such omissions may be corrected in succeeding reviews.

PERNICIOUS ANEMIA

General Considerations—It is generally accepted that achlorhydria is a constant feature of pernicious anemia and that the intrinsic factor of Castle is present in decreased amounts¹. Kahn² studied the case records of 840 persons with pernicious anemia. None of the patients secreted hydrochloric acid, and in none was there evidence of peptic ulcer.

The original work of Castle and his co-workers, in which they demonstrated that a specific antianemic substance, the "intrinsic factor,"

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan

1 Morrison, T H. The Role of the Gastric Secretion in Pernicious Anemia, *Internat Clin* **2** 131, 1937

2 Kahn, J R. Absence of Peptic Ulcer in Pernicious Anemia, *Am J M Sc* **194** 463, 1937

is produced in the wall of the stomach and is present in gastric juice but not in saliva or in the duodenal contents, indicated that the stomach alone of the gastrointestinal tract is the site of formation of the intrinsic factor. On strong theoretic grounds Thompson³ questioned this assumption and reported a number of cases of pernicious anemia and nontropical sprue in which treatment with desiccated duodenal mucosa of swine was successful. It is recognized that these observations cannot be construed as direct proof of the presence of the anti-anemic substance in human duodenal mucosa. Further studies on this point are indicated. Tempka⁴ fed 20 liters of saliva to a patient with pernicious anemia in relapse and observed reticulocyte response on the sixth day of treatment as well as symptomatic improvement. When the administration of saliva was discontinued, relapse occurred. The author stated the opinion that the hematologic changes were not the result of a spontaneous remission.

That interaction of the intrinsic and extrinsic factors is required for the normal maturation of red blood cells, although doubted by some, has never been disproved. Whether or not the intrinsic factor is present in the gastric juice of patients with pernicious anemia appears to be debatable. Fitz-Hugh and Creskoff⁵ stated the opinion that the substance is absent, but after a consideration of their data, their conclusions do not appear warranted. It appears more likely that the deficiency of the intrinsic factor is quantitative rather than qualitative. Fouts, Helmer and Zerfas⁶ showed that patients with pernicious anemia have a decrease of gastric secretion that is directly proportional to the level of the red blood cell count. They also concluded that the amount of fasting gastric content is dependent on the age of the patient, the presence and severity of changes in the central nervous system and the amount and type of antecedent therapy. Their observations were similar to those of Goldhamer⁷ but are open to a different interpretation. Goldhamer stated that the gastric secretion in relapse is dependent primarily on the severity of the disease process and less on the age of the subjects, whereas in remission the gastric volume appears to be

3 Thompson, J. C. Hematopoietic Response Following Oral Administration of Desiccated Duodenal Mucosa, *Ann Int Med* **11** 39, 1937.

4 Tempka, T. Die Bedeutung der Speicheldrüsen für die Pathogenese der Biermerschen Krankheit, *Folia haemat* **57** 30, 1937.

5 Fitz-Hugh, T., Jr., and Creskoff, A. J. Experiments with "Depepsinized" Human Gastric Juice in Treatment of Pernicious Anemia, *Am J M Sc* **192** 168, 1936.

6 Fouts, P. J., Helmer, O. M., and Zerfas, L. G. Gastrointestinal Studies. Volume of Gastric Juice in Pernicious Anemia, *Am J Digest Dis & Nutrition* **3** 904, 1937.

7 Goldhamer, S. M. The Gastric Juice in Patients with Pernicious Anemia in Induced Remission, *Am J M Sc* **193** 23, 1937.

correlated with age. In addition to the volumetric studies it was shown that the combined juice of patients in relapse contained the intrinsic factor.

Several interesting experiments have been performed in an effort to determine the nature of the intrinsic factor. Helmer and Emerson,⁸ in studying the interaction between the intrinsic and the extrinsic factor on incubation with liver extract and normal gastric juice, noted only a slight proteolytic effect, which they attributed to be due to peptic activity. Taylor and his co-workers⁹ observed some alterations in casein metabolism with normal gastric juice at a p_H of 7.4 and concluded that the changes were due to activity of the intrinsic factor. They did not imply that casein was the extrinsic factor. Helmer and Fouts¹⁰ demonstrated that the intrinsic factor in gastric juice could be precipitated with saturated ammonium sulfate and that it was nondialyzable and was insoluble in 80 per cent alcohol.

Hernberg¹¹ demonstrated the presence of the intrinsic factor in the gastric contents of patients with anemia due to *Bothriocephalus*. Stasney and Higgins¹² injected concentrated gastric juice into pregnant rats. From observations of the number and the structure of the fetal erythrocytes before and after administration of gastric juice to the mothers, they concluded that they could detect the presence of the substance causing the development of the red blood cells. Mark and Hauke¹³ also used the rat for the determination of the intrinsic factor in gastric juice. It was their conclusion that if reticulocytosis is obtained in this animal after the parenteral administration of gastric juice, the person from whom the gastric juice is obtained does not have pernicious anemia. If no reticulocyte response is observed, the patient may or

8 Helmer, O. M., and Emerson, C. P. Studies on the Chemical Nature of the Interaction Between the Intrinsic and Extrinsic Antianemic Factors upon Incubation of Liver Extract and Normal Gastric Juice, *Am J Digest Dis & Nutrition* **3** 906, 1937.

9 Taylor, H. L., Castle, W. B., Henle, R. W., and Adams, M. A. Correlation of in Vitro Activity of Normal Human Gastric Juice on Casein at p_H 7.4 with Gastric Intrinsic Factor, *Proc Soc Exper Biol & Med* **36** 566, 1937.

10 Helmer, O. M., and Fouts, P. J. Fractionation Studies on Intrinsic Factor in Normal Human Gastric Juice, *Am J M Sc* **194** 399, 1937.

11 Hernberg, C. A. Concerning the Anti-Anaemic Influence of the Gastric Juice in Pernicious *Bothriocephalus* Anaemia, *Acta med Scandinav*, 1936, supp 78, p 582.

12 Stasney, J., and Higgins, G. M. The Effect of Normal Human Gastric Juice Administered to the Mother on the Size and Volume of the Erythrocytes of the Fetus, *Proc Staff Meet, Mayo Clin* **12** 490, 1937.

13 Mark, R. E., and Hauke, G. Ueber den Nachweis des Castleschen Fermentes im Magensaft bei Anämien, *Ztschr f klin Med* **132** 705, 1937.

may not have pernicious anemia Wills, Clutterbuck and Evans¹⁴ studied the macrocytic anemias of monkeys and concluded that both the intrinsic and the extrinsic factor are necessary for normal erythrogenesis

The extrinsic factor of Castle has been found in a number of protein-containing foods, such as beef muscle, autolyzed yeast, wheat germ and egg white On the other hand, casein has been reported by Castle and Townsend as giving a negative reaction with the intrinsic substance when incubated with gastric juice at a p_H of 2.5 to 3.5 Miller and Pritchard¹⁵ argued that since infants may be maintained on milk alone for long periods without developing pernicious anemia, it might be assumed that caseinogen, the chief protein of milk, probably contains the extrinsic factor To test this hypothesis they treated with whole milk and gastric juice 2 patients with pernicious anemia, while maintaining them on a diet devoid of known sources of extrinsic factor Fair hematologic responses were obtained in both cases, indicating the presence of extrinsic factor in the milk Three other patients failed to respond to a mixture of gastric juice and whey, thereby suggesting that the extrinsic factor of milk is contained within the casein portion However insufficient amounts of whey may have been used in the mixture tested

An attempt was made by Ungley¹⁶ to secure a more potent liver fraction by supplementing the purification method of Dakin and West A product prepared according to the method of Dakin and West (anahaemin) was first dissolved in phenol, anhydrous methyl alcohol was then slowly added so as to effect fractional precipitation The first fraction was eliminated and the latter one retained The resulting product was a light buff and contained 14.3 per cent nitrogen Twenty patients with pernicious anemia were given this material to determine the minimum effective dose, and in 5 cases the double reticulocyte response was employed to compare its strength with that of the original preparation It was found that a dose of 50 to 75 mg gave results comparable to those obtained from 200 mg of the original product After the use of the double reticulocyte method, Ungley concluded that the potency of 2 mg of the more purified fraction was greater than that of 5 mg of the original preparation

14 Wills, L., Clutterbuck, P. W., and Evans, B. D. F. A New Factor in the Production and Cure of Certain Macrocytic Anaemias, *Lancet* **1** 311, 1937

15 Miller, F. R., and Pritchard, W. H. Presence in Milk of the Extrinsic Factor of Castle, *Proc Soc Exper Biol & Med* **37** 149, 1937

16 Ungley, C. C. Further Purification of Dakin and West's Liver Fraction Purified Anahaemin Compared with Original Product in Regard to Effect in Pernicious Anemia, *Lancet* **2** 1513, 1936

Jacobson and Subbarow¹⁷ suggested that the therapeutic activity of liver extract may depend on the presence of a number of chemically distinct substances. They said they believed that several accessory factors augment the activity of the primary factor. Of the three known accessory factors, one is L-tyrosine, another contains a complex purine and the third is a peptide. The chemical nature of the primary factor is undetermined. Without the activity of the primary factor the accessory factors are therapeutically inert, whereas the primary factor alone is only slightly active. The materials tested were given intramuscularly to patients with pernicious anemia in relapse, and evidence in support of the authors' hypothesis was derived in part from data concerning the production of reticulocytes but principally from observations of regeneration of erythrocytes.

Although the chemical identity of the essential substance in preparations therapeutically active against pernicious anemia is not known, Jacobs¹⁸ attempted to synthesize substances which he said he had reason to believe resembled those present in potent liver extract. As a basis for the selection of the materials used in his experiments he employed the reaction with alkaline solution of trinitrophenol. A positive reaction consists of the reddening of the solution by the test substance after ten to fifteen minutes of heating in a boiling water bath. The gastric content of normal persons during fasting gave a positive reaction, whereas that of persons with pernicious anemia did not. Likewise all purified preparations active against pernicious anemia yielded a positive reaction to trinitrophenol. Because some of the properties of liver extract suggest that its activity may depend on a phenomenon of oxidation-reduction and that the essential substances involved may be an aldehyde derivative and dextrosamine, Jacobs employed intramuscular and subcutaneous injections of these substances in the treatment of patients with pernicious anemia in relapse. When either substance was given alone no reticulocyte response was obtained, but in 1 case he obtained a reticulocyte count of 14 per cent five days after the subcutaneous injection of a water solution of the product of interaction between acetaldehyde and dextrosamine. Three other previously untreated patients failed to respond to this treatment. Jacobs¹⁹ has isolated a crystalline substance from liver extract which he concluded

17 Jacobson, B. M., and Subbarow, Y. Studies of the Principle in Liver Effective in Pernicious Anemia, Therapeutic Activity of Its Multiple Factors, *J. Clin. Investigation* **16** 573, 1937.

18 Jacobs, H. R. On the Nature of the Antipernicious Anemia Principle, *J. Lab. & Clin. Med.* **22** 371, 1937.

19 Jacobs, H. R. On the Nature of the Antipernicious Anemia Principle II. Identification of the 5, 6-Quinone of Dihydroindole-2-Carboxylic Acid in Liver Extract, *J. Lab. & Clin. Med.* **22** 890, 1937.

is identical with the 5,6-quinone of dihydroindole-2-carboxylic acid obtained by Rafei from the reactions of tyrosinase and tyrosine. Because this substance is difficult to synthesize in pure form, Jacobs²⁰ employed in the treatment of 1 patient with pernicious anemia the "red substance" obtained from the action of tyrosinase on tyrosine in the presence of oxygen. The reticulocyte response was equivocal but sufficiently suggestive of activity to warrant further trial.

The fact that some patients with pernicious anemia respond much more favorably to the parenteral injection of liver extract than to its oral administration led Helmer and Fouts²¹ to attempt to measure the absorptive ability of the intestinal tract by estimations of the urinary excretion of xylose. This sugar is not metabolized and is believed to pass through the liver unchanged and to escape from the body through the kidneys. The authors were unable to demonstrate in patients with pernicious anemia a consistent abnormality in the absorption of xylose from the alimentary tract. However, owing to the great difference between the molecular weight of the active principle of liver and that of xylose, the authors concluded that ability to absorb xylose does not necessarily parallel the absorptive capacity for the antianemic principle. Fouts, Helmer and Zervas²² studied the secretion of hippuric acid in cases of pernicious anemia after the injection of sodium benzoate. This test is regarded as a measure of the detoxifying function of the liver. In their cases there was no obvious correlation between the level of the red blood cell count and the amount of hippuric acid secreted by the kidneys. There was, however, a direct relation between the quantity recovered from the urine and the renal function as measured by the urea clearance test. They concluded that both decreased secretion of hippuric acid and increased requirement of liver extract for maintenance of normal blood values are the result of complicating factors such as senility, infection and changes in the spinal cord. Impaired hepatic function, as indicated by the decreased ability of the liver to conjugate benzoic acid, had no apparent influence on the maintenance requirement of liver extract.

The problem of bioassay of preparations proposed for the treatment of pernicious anemia has attracted a number of investigators. Among the animal tests suggested during recent years is the reticulocyte

20 Jacobs, H. R. On the Nature of Anti-Pernicious Anemia Principle. Response of a Case of Pernicious Anemia to the Oral Administration of Tyrosinase-Tyrosine Mixture, *J. Lab. & Clin. Med.* **22** 892, 1937.

21 Helmer, O. M., and Fouts, P. J. Gastrointestinal Studies. Excretion of Xylose in Pernicious Anemia, *J. Clin. Investigation* **16** 343, 1937.

22 Fouts, P. J., Helmer, O. M., and Zervas, L. G. Secretion of Hippuric Acid in Pernicious Anemia, *Am. J. M. Sc.* **193** 647, 1937.

response of normal stabilized guinea pigs to the administration of potent antianemic material. This test, formulated and employed by Jacobson, has not met with general favor. After careful studies Hummel²³ concluded that the percentage of reticulocytes in the circulating blood of the guinea pig increases after a variety of disturbances, such as dietary changes, pregnancy, injury and infection. Occasionally rises occur for which no cause can be found. By suitable care in handling and feeding, stable reticulocyte levels may be maintained for as long as three months. It was possible to demonstrate increases in the reticulocyte count after the oral administration of a potent liver extract, and such responses did not occur when the active principle had been destroyed. However, the author said he did not believe that his observations proved the validity of the guinea pig reticulocyte test for the therapeutic activity of liver preparations, since the question of which constituent of liver is effective in producing the response must await further investigation. Even less satisfactory results with the guinea pig assay method were reported by Bachrach and Fogelson²⁴. From their observations and from a review of the literature they concluded that no animal can supplant the human being with pernicious anemia as a basis for the assay of potency of substances against pernicious anemia.

Evidence against the efficacy of parenteral injections of congo red, both in the induction of remissions and in the maintenance therapy of patients with pernicious anemia, was reported by Lendvai²⁵ and by Barker²⁶. After extensive observations both investigators concluded that the dye is totally ineffective in the treatment of patients with pernicious anemia.

Granady²⁷ reported 4 cases of pernicious anemia occurring in Negroes and said that the condition is not as rare in this race as has been commonly supposed. His patients appeared to have all the signs and symptoms necessary to establish the diagnosis of pernicious anemia, and in addition each showed a satisfactory response after the administration of specific therapy. No mention was made as to whether or

23 Hummel, L. E. Liver Extract and Reticulocytosis in the Guinea Pig, *Proc Soc Exper Biol & Med* **36** 657, 1937.

24 Bachrach, W. H., and Fogelson, S. J. Effect of Anti-Pernicious Anemia Substances upon Guinea Pig Reticulocytosis and a Review of the Literature, *J Lab & Clin Med* **22** 925, 1937.

25 Lendvai, J. Die Wirkung von Kongorot bei perniziöser Anämie, *Klin Wchnschr* **15** 1034, 1936.

26 Barker, W. H. Congo Red in Treatment of Pernicious Anemia and Sprue, *Am J M Sc* **194** 293, 1937.

27 Granady, J. T. W. Pernicious Anemia in Negro with Report of Four Cases, *J Nat M A* **29** 9, 1937.

not the patients were mulattoes. It is not so rare to observe pernicious anemia in persons with a mixture of white and Negro strains, but the occurrence of the disease in one of proved pure Negro stock is difficult to substantiate.

Five patients with pernicious anemia were studied by Stewart, Crane and Deitrick²⁸ in order to observe the adjustment of the heart to a slowly developing decrease in the oxygen capacity of the blood. Observations of the cardiac output determined by the acetylene method were made during the stage of anemia and were repeated during a therapeutically induced remission. Their findings were as follows:

During the anemic state the cardiac output, the heart rate, and the oxygen consumption were in all cases elevated, and the circulation time short. As the anemia became less, the cardiac output, the heart rate, and the oxygen consumption decreased, and the circulation time increased, all approaching more nearly normal values.

From these observations the authors concluded that during the stage of anemia in pernicious anemia the heart is required to circulate an increased amount of blood per minute. The amount of the increase is inversely proportional to the concentration of hemoglobin.

Stalker²⁹ reviewed the literature dealing with the occurrence of angina pectoris in patients with pernicious anemia and reported a single case. Statistics were cited to indicate that this is not a common complication, since a study of large groups of patients with pernicious anemia showed that only 2 to 3 per cent had angina. As the two diseases occur in the same age groups it is not surprising that they should have a coincidental coexistence. Although the author said he recognized that anoxemia resulting from anemia diminishes the function of the myocardium and so furthers the occurrence of anginal attacks, he said he believed that anemia alone cannot cause angina pectoris but that in addition there must always be disease of the coronary arteries. The findings in the case reported substantiate this view.

McGregor³⁰ described 2 patients with pernicious anemia and diabetes mellitus and reviewed the literature concerning the coexistence of the two diseases. He quoted figures which indicate that between 0.5 and 1 per cent of all patients with pernicious anemia also have diabetes. In explaining why the two diseases may exist in the same

28 Stewart, H. J., Crane, N. F., and Deitrick, J. E. Studies of Circulation in Pernicious Anemia, *J. Clin. Investigation* **16** 431, 1937, abstracted, *Tr. A. Am. Physicians* **51** 84, 1936.

29 Stalker, H. Angina Pectoris and Pernicious Anemia (Old Terminology) Resume of the Literature, with a Case Report, *Ann. Int. Med.* **10** 1172, 1937.

30 McGregor, H. G. Pernicious Anemia with Diabetes Mellitus, *Brit. M. J.* **2** 617, 1937.

patient he referred to Root, who has pointed out factors which may predispose to their combined incidence, as follows. Achlorhydria, which is practically always present in cases of pernicious anemia, is not a rare finding in cases of diabetes, diabetes occurs most commonly in the same age groups as does pernicious anemia, and, finally, the familial tendency is well recognized in both diseases. In spite of a certain amount of common ground between the two conditions, the authors said they regarded this association as one of chance.

Changes in the Blood and Bone Marrow—Schjødt,³¹ following the work of Riddle, applied Robertson's simple growth equation to the regeneration of erythrocytes in pernicious anemia and in other types of anemia. The curve of regeneration during treatment with desiccated stomach or liver extract is, in general, in accord with the growth equation, although a temporary end point somewhat lower than the normal level of the red blood corpuscles must be assumed. Ornstein and Schouten³² studied the duration of life and mode of death of erythrocytes in patients with pernicious anemia before and after treatment with liver. The mean age of the cells during relapse is much less than that in remission. In the former state the anomalous cells have a mortality rate practically independent of their age, and their destruction is random and fortuitous. Normal individual corpuscles, on the other hand, are destroyed at an age closely approximating their mean span of life.

On the assumption that the action of the antianemic principle is concerned with the formation of erythrocyte stroma rather than hemoglobin synthesis, Williams and his colleagues³³ studied the chemical composition of the cells and plasma before and after treatment. They found that the sodium, potassium and chlorine contents of the serum and erythrocytes were unaffected in pernicious anemia. However, during relapse there was an increased amount of neutral fat in the serum, with an associated deficiency of cholesterol esters and phospholipid. The lipid values returned to normal after treatment. A study of erythrocytes showed that they contained an excessive amount of cholesterol esters and a deficiency of phospholipid and free cholesterol. Both the cation and the anion content were elevated, the former being due chiefly to the increased potassium and the latter to a greater hemoglobin con-

31 Schjødt, E. Regeneration of Blood, Expressed by Simple Equation, *Acta med Scandinav*, 1936, supp 78, p 195

32 Ornstein, L. S., and Schouten, J. F. The Duration of Life and the Mode of Death of Erythrocytes Before and After the Treatment of Pernicious Anemia with Liver, *Nederl tijdschr v geneesk* **81** 1717, 1937

33 Williams, H. H., and others. Lipid and Mineral Distribution of Serum and Erythrocytes in Pernicious Anemia Before and After Therapy, *J Biol Chem* **118** 599, 1937

tent During remission both the lipid and the mineral content of the red blood cells became normal. The authors suggested that the chemical composition of the abnormal erythrocytes in pernicious anemia during relapse indicates that the cells not only are in a state of lowered function but are in process of degeneration and retrogression.

Bang and Ørskov³⁴ studied the permeability of the red blood cells to dextrose in 10 patients with pernicious anemia, and in 7 the permeability was tested periodically during the course of treatment. They found that during relapse the permeability of the erythrocytes is increased to as much as four times the average normal value. When the anemia disappears as a result of treatment, the permeability becomes normal. The explanation of the changes during treatment is uncertain, but the following factors should be considered: (1) an alteration in the membrane of the circulating red blood cells, (2) the formation of large numbers of young red blood cells with low permeability and (3) a diminished destruction of red blood cells, with a resultant rise in the average age of the circulating erythrocytes.

The production and excretion of bile pigment in pernicious anemia may be due to increased rate of destruction of hemoglobin, or it may result from partial or total pathologic metabolism of the precursors of hemoglobin. In order to investigate this problem Dobriner and Barker³⁵ studied the excretion of coproporphyrin I of a patient with pernicious anemia in relapse and during the return of the red blood cells and hemoglobin to normal. They demonstrated a definite increase in the amount of coproporphyrin I in the urine and feces during relapse and found that lower values were present when the blood reached normal limits. These observations suggested to the authors that in pernicious anemia there is an increase in the production of coproporphyrin I proportional to an increased formation of type III porphyrin rather than a pathologic production resulting in a disturbed ratio between the formation of type I and that of type III compounds.

Weil³⁶ said he believed that in pernicious and other hyperchromic anemias there is a familial, hereditary or acquired "hematic soil," characterized by a pathologic tendency of both the bone marrow and the upper portion of the gastrointestinal tract. A similar mechanism is claimed for *aleucie hémorrhagique* and total medullary aplasia.

34 Bang, O., and Ørskov, S. L. Variations in the Permeability of Red Blood Cells in Man, with Particular Reference to Conditions Obtaining in Pernicious Anemia, *J. Clin. Investigation* **16** 279, 1937, *Hospitaltid* **80** 141, 1937.

35 Dobriner, K., and Barker, W. H. Total Coproporphyrin I Excretion in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **36** 864, 1937.

36 Weil, P. E. Le terrain morbide dans le Biermer et les états d'aplasie médullaire, *Sang* **11** 783, 1937.

Dameshek and Valentine³⁷ studied the sternal bone marrow of 20 patients with pernicious anemia before and after specific therapy. Twenty-six biopsies were done, and the results were correlated with the status of the peripheral blood and with the response to treatment. The biopsies were performed by Seyfarth's technic, in which a small trephine is employed. A definite correlation was found between the marrow and the blood picture for, generally speaking, the lower the red blood cell count, the more primitive and hyperplastic the marrow. The marrow of patients with pernicious anemia during relapse uniformly showed marked hyperplasia, with complete replacement of fat by proliferating cells. In most cases, especially those in which there was severe anemia, the hyperplasia was due primarily to a marked increase of cells of the megaloblastic series, although myeloid proliferation was also always found. There were also present large numbers of erythrogones (promegaloblasts) and sometimes even more primitive cells than those which resembled histiocytes. Little tendency toward maturation of the red blood cells was apparent, for nucleated red blood cells of the more mature types were present only in small numbers. The megakaryocytes in the blood of patients with low red blood cell counts were greatly diminished in number or were absent. When the patients received liver therapy, striking alterations occurred within twenty-four hours after treatment was begun. The marrow picture rapidly changed to one in which the normoblast was the predominating cell. There was also a disappearance of the misshapen giant polymorphonuclear neutrophils. On the other hand, observations somewhat at variance with those of Dameshek and Valentine were reported by Storti³⁸. He studied the bone marrow of 4 patients with pernicious anemia at intervals before and after liver therapy. Besides the arrest at the megaloblast stage, he noted that the normoblast tissue was equal to or greater than that of normal marrow. With the approach of the height of the reticulocyte response there is a disappearance of megaloblastic tissue, and hemopoiesis proceeds by the normoblastic route. The antianemic principle, he found, does not produce a normoblastic proliferation but causes a ripening of the preexisting normoblasts and a reduction of the megaloblastic tissue.

37 Dameshek, W., and Valentine, E. H. Sternal Marrow in Pernicious Anemia. The Correlation of Observations at Biopsy with Blood Picture and Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, *Arch Path* **23** 159 (Feb) 1937.

38 Storti, E. Studio in vivo del midollo osseo nell'anemia perniciosa, sulle primissime modificazioni morfologico-funzionali del tessuto mieloide conseguenti a epatoterapia, *Haematologica* **18** 1, 1937.

Biopsy specimens of bone marrow from patients with pernicious anemia were studied by Jones³⁹ with particular reference to the origin and development of neutrophils. He concluded that in pernicious anemia during relapse there is panmyelopathy. The proliferation of megakaryoblasts in this disease is regarded as a pathologic developmental form, rather than the result of inhibition of maturation at the megakaryoblast stage, which is the more common view held in this country. In confirmation of Storti's observations, Jones found evidence of actual increase in the total number of normoblasts in the marrow of patients with pernicious anemia, and he concluded that there is inhibition of maturation of these cells. Alterations in the neutrophils, hyperpolymorphism, hypersegmentation and gigantism are not considered as degenerative manifestations but as evidence of a pathologic neutrophil series. Likewise, the megakaryocytes are pathologically altered so that there is partial failure of production of platelets. It is suggested that a lack of the antianemic principle may have its primary effect on the stem cell or even on the reticuloendothelium.

Manifestations Due to Lesions in the Spinal Cord and Brain and Practical Therapy—In recent years the major problem in caring for patients with pernicious anemia has been the prevention and treatment of lesions of the central nervous system. It is generally accepted that degeneration of the spinal cord and brain is part of the disease process. Herman, Most and Jolliffe⁴⁰ studied 255 patients with pernicious anemia. Involvement of the spinal cord was present in 72.5 per cent of their cases, and psychotic changes were observed in 15.7 per cent.

In an attempt to explain the obscure etiology of the pathologic changes in the central nervous system due to anemia, Heymans and his associates⁴¹ performed some interesting experiments on isolated perfused dog heads. They concluded that certain nerve centers, probably located in the cerebrum, are apparently necessary for continued survival of the animal. These centers are especially sensitive to anoxemia and are irreparably damaged after circulatory arrest is maintained for five minutes or longer. Although such conditions are not present in pernicious anemia, it is conceivable that prolonged anemia itself may aid in the production or development of pathologic changes in the cen-

39 Jones, O. P. Origin of Neutrophiles in Pernicious Anemia (Cooke's Macropolycytes). Biopsies of Bone Marrow, *Arch Int Med* **60** 1002 (Dec) 1937.

40 Herman, M., Most, H., and Jolliffe, N. Psychoses Associated with Pernicious Anemia, *Arch Neurol & Psychiat* **38** 348 (Aug) 1937.

41 Heymans, C., Bouckaert, J. J., Jourdan, F., Nowak, S. J. G., and Farber, S. Survival and Revival of Nerve Centers Following Acute Anemia, *Arch Neurol & Psychiat* **38** 304 (Aug) 1937.

tral nervous system. However, anemia cannot be regarded as the sole cause of the degeneration of the nervous tissue. Woltman and Heck⁴² pointed out that funicular degeneration of the spinal cord may exist in at least sixty conditions other than pernicious anemia. Golden⁴³ emphasized the importance of diet in the prevention of nervous disorders and discussed the role of various food factors both in the production and in the treatment of these disorders. Some evidence supporting the relation of food metabolism and degeneration of the spinal cord may be gained from the case report of Lacroix and Koek.⁴⁴ They observed the development of macrocytic anemia and manifestations of involvement of the spinal cord in a patient nine years after extensive resection of the stomach. Satisfactory improvement was obtained with parenteral administration of liver extract and vitamin B therapy.

Conclusions drawn from apparent therapeutic results should be guarded, as it is known that spontaneous variations occur in the intensity of the neurologic manifestations without any medication. It is generally agreed that adequate antianemic therapy is of primary importance in the treatment of lesions of the spinal cord. Criteria of adequacy include elevations of erythrocyte and hemoglobin values to normal levels and maintenance of the normal size of the red blood cell. Hitzengerber⁴⁵ advocated massive doses of both liver and stomach preparations and recommended the use of supplementary vitamins. In addition to medicinal therapy, Hyland and Farquharson⁴⁶ recommended long periods of rest. In their opinion the combination of adequate medication and prolonged rest prevents changes in the central nervous system, it arrests the progress of any existing pathologic condition of the cord and it effects considerable improvement, especially in anemia of short duration.

Moench⁴⁷ studied a group of 32 patients with pernicious anemia to determine the amount of therapy necessary to maintain the red blood cell count at a normal level and the length of time required to bring

42 Woltman, H. W., and Heck, F. J. Funicular Degeneration of the Spinal Cord Without Pernicious Anemia, *Arch Int Med* **60** 272 (Aug) 1937.

43 Golden, L. A. The Role of Diet in Nervous Diseases. New Orleans M. & S. J. **90** 73, 1937.

44 Lacroix, W., and Koek, H. C. Case of Hyperchromic Anemia with Neurologic Symptoms Developing After Resection of Stomach, *Nederl tijdschr v geneesk* **81** 2221, 1937.

45 Hitzengerber, K. Zur Behandlung der neurologischen Komplikationen der Anaemia Perniciosa, *Wien med Wchnschr* **87** 257, 1937.

46 Hyland, H. H., and Farquharson, R. F. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, *Arch Neurol & Psychiat* **36** 1166 (Dec) 1936.

47 Moench, L. M. Variations in Response to Therapy in Pernicious Anemia, *Ann Int Med* **10** 1115, 1937.

the count to 4,500,000 per cubic millimeter. The average length of the maintenance period was twenty-one months, the shortest period being five and the longest fifty months. Therapy consisted of the intramuscular injection of an average monthly dose of the amount of a commercially prepared concentrated liver extract derived from 300 Gm of liver or unconcentrated extract obtained from 200 Gm of liver prepared in the laboratories of the New York Hospital. This dosage maintained the red blood cells of 70 per cent of the patients above the minimum normal red blood cell level of 4,900,000 for men and 4,400,000 for women. The red blood cell counts of the remaining 30 per cent of these patients were only slightly reduced, varying between 3,600,000 and 4,600,000 for 5 men and between 3,900,000 and 4,200,000 for 5 women. In 8 of this group the disease appeared to be fully controlled as far as symptoms and signs were concerned. In 1 patient there was slow progression of changes in the central nervous system, and in another there was no relief from the symptoms of which he had originally complained. All the women and 3 of the men received approximately twice the usual amount of intramuscular therapy, and 2 received supplementary liver orally. On the other hand, the author reported that for 1 patient the blood was maintained at a normal level for a year in spite of the fact that he was receiving intramuscularly the extract derived from only 150 Gm of liver. Since this followed a period of heavy dosage the author said he considered it as evidence of gradual storage of active principle which subsequently yields a hemopoietic effect.

Observations were also made by Moench to determine the time required for the erythrocyte count to reach 4,500,000 and the amount of liver preparation used. Fifteen of the 33 patients, with an average initial red blood cell count of 2,600,000, received by intramuscular injection the amount of extract derived from an average of 670 Gm of liver, and the red cell count reached 4,500,000 in two months or less. There were 11 patients with an average initial count of 1,900,000 for whom more than two months but less than three months was required before this level was reached. They received intramuscularly the extract derived from an average of 1,072 Gm of liver. A third group, consisting of 7 patients, required from four to nine months for the red blood cells to attain a level of 4,500,000. They received intramuscularly the extract derived from 900 to 6,600 Gm of liver. For some of these patients the dosage was considered insufficient, others were suffering from senility, malnutrition, depressions or infection, such as sinusitis. It was emphasized by the author that symptoms referable to the nervous system are the most serious and persistent

In slightly over half the patients there was subjective improvement. Seventeen of 26 patients who had objective changes of the nervous system showed "apparent improvement" as judged by the clinic records. Such a high percentage of patients showing objective evidence of improvement in the manifestations of involvement of the central nervous system is not in accord with the observations of other clinicians.

Hartfall⁴⁸ reported therapeutic results for 16 patients with pernicious anemia in relapse and 20 patients receiving maintenance treatment. Intramuscular injections of a concentrated liver extract, 1 cc derived from 100 Gm of liver, were employed exclusively. In all cases 2 to 5 cc of this preparation produced a satisfactory reticulocyte response. Subsequent treatment with 1 to 2 cc at weekly intervals sufficed to elevate the red blood cell count to 4,000,000 or above in twenty-one to thirty-five days except in cases of anemia complicated by infection. Satisfactory maintenance treatment consisted of the administration of 1 cc of the concentrated extract at intervals varying from three to eight weeks. Individual variations of maintenance requirement were emphasized by the author. The incidence and the severity of neurologic lesions of the patients in Hartfall's series were relatively slight. Improvement in nervous symptoms was noted after induction of remission in the few cases in which there was involvement of the central nervous system.

Mulholland⁴⁹ reported a case of pernicious anemia in a man aged 62 in whom there was a prompt and characteristic response to the intramuscular injection of liver extract. After a subsequent relapse, attributed to inadequate dosage of liver extract, he was treated with 32 cc of potent extract by intramuscular injection over forty-five days and received in addition stomach U S P for ten days and liver by mouth for thirty days of this period. During this time no significant reticulocyte response occurred, and there was a decline of both red blood cells and hemoglobin. Subsequently, he was given five intravenous injections each of 20 cc of liver extract derived from 100 Gm of liver. After forty days the erythrocyte count was 4,500,000 and the hemoglobin value 76 per cent. Maintenance of these values was then effected by the intramuscular injection of 2 cc of liver extract per week. No explanation of the lack of response to intramuscular therapy is offered. Failure to absorb the intramuscular preparation seems unlikely in view of the subsequent satisfactory control of the condition with this mode of therapy.

48 Hartfall, S. J. Experiences with Concentrated Whole Liver Extract, *Lancet* **2** 317, 1937.

49 Mulholland, H. B. Intravenous Liver Extract in Therapy of Pernicious Anemia. Report of a Case, *Ann Int Med* **11** 671, 1937.

Sellers⁵⁰ made the statement that prior to the introduction of liver in the treatment of pernicious anemia the average duration of life after the diagnosis was made was estimated at two to two and one-half years. Now it is generally agreed that with proper liver therapy the fatal termination may be postponed indefinitely in a majority of cases. He quoted Stocks as stating that since 1926, when liver treatment was introduced, there has been "an average lengthening of life of all persons affected with pernicious anemia in England and Wales of about three to three and one-half years." This does not give the true life expectancy, because it includes persons who were adequately treated as well as those who, for one reason or another, failed to receive adequate specific treatment prior to the terminal illness. The author pointed out that wide differences in mortality from pernicious anemia exist throughout the world for reasons which are not apparent. For example, in 1926 the mortality rate in Norway was 5.4 and in Ontario during the same year the rate was 15.9 per hundred thousand. In the countries where data were obtained (Norway, the United States, New Zealand, England, Wales, Scotland, Canada and the province of Ontario) there was an abrupt drop in the mortality rate in 1927, coinciding with the general use of liver in the treatment of the disease. This reduction has been well maintained. In Ontario, for example, the standardized specific mortality in 1934 was only 4.7 per cent of the average level for the period prior to the introduction of liver therapy. The reduction of mortality has been apparent in all age groups up to 70 years, but it has been most marked in youth. Sellers concluded:

Comparison of the actual average age at death of persons dying of pernicious anemia in Ontario with that to be "expected" on the basis of specific mortality experience in the period prior to liver therapy, 1921-1926, shows that the net increase in the average age of death amounted in 1934 to 5.3 years in males and to 5.1 years in females.

During the period from 1921 to 1935, inclusive, there were 6,223 deaths from pernicious anemia among the policy holders of the Metropolitan Life Insurance Company (Dublin and Lotka⁵¹), an incidence of 0.3 per cent of all deaths; there were 1,787 white males, 150 Negroes, 4,015 white females and 271 Negresses. The death rate from pernicious anemia was 2.5 per hundred thousand.

50 Sellers, A. H. A Study of the Objective Efficacy of Liver Therapy in Pernicious Anemia Based on Recorded Mortality Data, *Am J Hyg* 25:259, 1937.

51 Dublin, L. I., and Lotka, A. J. Twenty-Five Years of Health Progress. A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company 1911 to 1935, New York, Metropolitan Life Insurance Co., 1937, p. 533.

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

Recent reviews by Goldhamer and his associates⁵² and by Brown⁵³ emphasized some of the etiologic factors which may lead to macrocytic anemia. A substance necessary for the maturation of red blood cells is produced apparently by the interaction of a dietary and a gastric intrinsic factor. The product so formed is absorbed from the intestine, it passes through and is modified by the liver and is utilized by the bone marrow as needed. Macrocytic anemia will result if there is disturbance of any of the steps involved in this mechanism.

Thus far the extrinsic factor has not been identified. Elsom⁵⁴ observed the development of macrocytic anemia in pregnant women receiving a diet deficient in vitamin B. The anemia responded readily to the addition of yeast or to the intramuscular administration of liver extract. Two patients with features simulating pernicious anemia who had received a deficient diet for a long time were described by Groen and Snapper⁵⁵. Both secreted free hydrochloric acid, but the quantity of gastric juice was decreased. One responded to liver therapy and the other to autolyzed yeast. The authors concluded that the macrocytic anemia in these cases was the result of a deficiency of the extrinsic factor.

Langmead and Doniach⁵⁶ described the case of a 13 month old child who, they believed, showed the necessary requirements for a diagnosis of pernicious anemia. The development of pernicious anemia in a woman who drank nitric acid was reported by Alsted⁵⁷. In his opinion the atrophy of the gastric mucosa due to the nitric acid resulted in failure of production of the intrinsic factor. Lake⁵⁸ reviewed reports of 320 cases in which gastrectomy had been performed for various causes. In none of these cases did macrocytic anemia develop, although an occasional case of microcytic anemia was observed. In 4 of a series

52 Goldhamer, S. M., Bethell, F. H., Isaacs, R., and Sturgis, C. C. Blood: A Review of the Recent Literature, *Arch. Int. Med.* **59**: 1051 (June) 1937.

53 Brown, C. L. Clinical Features of Macrocytic Anemias, *Pennsylvania M. J.* **40**: 922, 1937.

54 Elsom, K. O. Macrocytic Anemia in Pregnant Women with Vitamin B Deficiency, *J. Clin. Investigation* **16**: 463, 1937.

55 Groen, J., and Snapper, I. Dietary Deficiency as a Cause of Macrocytic Anemia, *Am. J. M. Sc.* **193**: 633, 1937.

56 Langmead, F. S., and Doniach, I. Pernicious Anemia in an Infant, *Lancet* **1**: 1048, 1937.

57 Alsted, G. Pernicious Anemia After Nitric Acid Corrosion of the Stomach, *Lancet* **1**: 76, 1937.

58 Lake, N. C. Partial Gastrectomy: A Review of Three Hundred and Twenty Cases, *Brit. M. J.* **2**: 49, 1937.

of 40 patients studied for five to twelve years after gastric resection for ulcer, Manizade⁵⁹ noted macrocytic anemia

In 1936 Israels and Wilkinson described a syndrome characterized by macrocytic anemia, free hydrochloric acid in the gastric contents, hyperplastic bone marrow and failure of response to antianemic therapy. The case of a 19 year old boy who exhibited all the features of this syndrome was reported by Abrahamson and Thompson,⁶⁰ who attributed the anemia to an intrinsic defect of the bone marrow. Wilkinson, Klein and Ashford⁶¹ demonstrated the presence of the hemopoietic substance in the livers of patients who died as a result of achrestic anemia. In their opinion, such anemia results from failure of the marrow to utilize the erythrogenic material.

Macrocytic anemia has been produced in animals by various methods. Rhoads⁶² fed indole to dogs on a deficient diet and observed hyperplasia of the marrow and macrocytic anemia. Liver extract was of both preventive and curative value. Substituting amidopyrine for indole, Rhoads and Miller⁶³ also succeeded in producing macrocytic anemia in dogs. Campanacci and Tosi⁶⁴ observed in rabbits after injections of hydroquinone, resorcinol, phenol or thyroxin, macrocytic anemia which could be prevented or cured by the parenteral administration of liver extract.

Mettier and Purviance⁶⁵ failed to produce macrocytic anemia in gastrectomized dogs by administering a diet deficient in vitamin B₂ and they were not able to influence the microcytic anemia resulting from

59 Manizade, M. D. Zur Frage der Anämie nach Magenresektion (Das Blutbild bei 40 magenresezierten Kranken, 5 bis 12 Jahre nach der Operation wegen Ulcus ventriculi oder duodeni), *Wien klin Wchnschr* **50** 1455, 1937

60 Abrahamson, L., and Thompson, A. Achrestic Anaemia, *Irish J. M. Sc.*, February 1937, p. 66

61 Wilkinson, J. F., Klein, L., and Ashford, C. A. Haemopoietic Activity of the Human Liver. Achrestic Anaemia and Aplastic Anemia, *Quart. J. Med.* **6** 143, 1937

62 Rhoads, C. P. Effect of Indol on Hematopoiesis in Dogs Fed Deficient Diets, *Proc. Soc. Exper. Biol. & Med.* **36** 652, 1937

63 Rhoads, C. P., and Miller, D. K. Effect of Diet on Susceptibility of Canine Hematopoietic System to Damage by Amidopyrine, *Proc. Soc. Exper. Biol. & Med.* **36** 654, 1937. Miller, D. K., and Rhoads, C. P. The Effect of Diet on the Susceptibility of the Canine Hematopoietic Function to Damage by Amidopyrine, *J. Exper. Med.* **66** 367, 1937

64 Campanacci, D., and Tosi, S. L'azione dell'epatoterapia nelle anemie tossiche sperimentali da sostanze aromatiche, *Gior. di clin. med.* **18** 391, 1937

65 Mettier, S. R., and Purviance, K. Effect of Artificial Achylia Gastrica and a Diet Restricted in Vitamin B₂ (G) on Hematopoiesis, *Proc. Soc. Exper. Biol. & Med.* **36** 429, 1937

removal of the stomach Hyperchromic anemia in swine following gastrectomy was reported by Waterman, Kok and Hirschfeld⁶⁶ The anemia was favorably influenced by the parenteral use of liver extract

ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

Hemolytic Anemia—The change in the size and the shape of the red blood cells in familial hemolytic icterus is considered by many to be a hereditary manifestation Dedichen⁶⁷ cited the history of 18 members of two families in support of this view Some writers are of the opinion that the alteration in the erythrocytes is due to lessened vitality of the cells, others believe that there is a primary defect of the bone marrow, and, finally, some suggest that the small red blood cells and the increased fragility are phenomena of regeneration secondary to the increased activity of the bone marrow The disease may occur in either sex, it has no racial distribution and it is transmitted by both males and females

Roentgenographic details of osseous changes, not uncommonly associated with this condition, have been described by Caffey⁶⁸ In the opinion of Acuña,⁶⁹ such alterations of the bones accompanying hemolytic anemia constitute a new disease that is probably related to the erythroblastic anemia of infancy

Since the treatment of familial hemolytic icterus is specific, it is important to differentiate this condition from other types of hemolytic anemia The latter can often be corrected with transfusions or by the elimination of specific drugs⁷⁰ or allergens⁷¹ Groag⁷² has pointed out that roentgen therapy is of no value in the treatment of the familial

66 Waterman, L, Kok, D J, and Hirschfeld, W K Experimental Hyperchromic Anemia After Gastric Resection, *Nederl tijdschr v geneesk* **81** 2622, 1937

67 Dedichen, H G Epidemic Occurrence of Anemic Crises in Hemolytic Jaundice, *Norsk mag f lægevidensk* **98** 279, 1937

68 Caffey, J Skeletal Changes in the Chronic Hemolytic Anemias (Erythroblastic Anemia, Sickle Cell Anemia and Chronic Hemolytic Icterus), *Am J Roentgenol* **37** 293, 1937

69 Acuña, M Alteraciones radiológicas del esqueleto en la ictericia hemolitica Congenita, *Prensa med argent* **24** 1878, 1937

70 (a) Kohn, S E Acute Hemolytic Anemia During Treatment with Sulfanilamide, *J A M A* **109** 1005 (Sept 25) 1937 (b) Harvey, A M, and Janeway, C A Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, *ibid* **109** 12 (July 3) 1937

71 Hutton, J E Favism An Unusually Observed Type of Hemolytic Anemia, *J A M A* **109** 1618 (Nov 13) 1937

72 Groag, P Ueber einen Versuch, den Blutbefund bei einem Fall konstitutioneller hamolytischer Anemie durch Kurzwellenbestrahlung der Milz zu beeinflussen, *Wien klin Wchnschr* **50** 502, 1937

type Sharpe⁷³ reported unsatisfactory results with iron and liver. It is generally agreed that splenectomy is desirable especially for patients who show marked anemia or who are subject to severe relapses. Although the anemia is corrected and the icterus disappears after removal of the spleen, microcytosis, spherocytosis and increased fragility persist. Resistance to hypotonic salt solution may increase after operation, but it does not become normal. Gordon, Kleinberg and Ponder⁷⁴ attributed the change in resistance after splenectomy to a modification of the structure of the envelop of the red blood cell.

Changes in the Blood Associated with Infection—Infection may cause a disturbance in the balance between the production and the destruction of the red blood cells. Usually hypochromic and microcytic anemia results, although macrocytic anemia is not uncommon. Gwyn⁷⁵ described such anemia associated with rheumatic infection. Giordano and Blum⁷⁶ reported 3 cases of acute hemolytic anemia (Lederer's type) and summarized reports of 52 other cases. They stated that the disease can occur at any age and in either sex. Its onset is usually sudden and is characterized by headaches, gastrointestinal upsets, abdominal pain and, after an incubation period of two to six days, severe anemia, pallor, icterus and fever. There may or may not be splenic or hepatic enlargement. Free acid is present in the gastric juice, there is no glossitis and the disease runs a rapid course. The anemia is macrocytic, with some evidence of regeneration. Leukocytosis with a leukemoid reaction is most common, but leukopenia may occur. Hyperbilirubinemia is present, associated with an increase in the excretion of urobilin and the appearance of free hemoglobin in the urine. The fragility of the red blood cells is within normal limits. Although infection is the suspected etiologic factor, it is not proved. Blood transfusions provide the only satisfactory means of treatment.

Studies of the blood in acute rheumatic fever were made by Massell and Jones⁷⁷. Although leukocytosis usually remained after the clinical manifestations had subsided, a normal white blood cell count might accompany clinical signs of active rheumatic fever. The authors concluded that the leukocyte count is nonspecific but that when it is elevated,

73 Sharpe, J. C. Hemolytic Jaundice, *Internat Clin* **2** 146, 1937.

74 Gordon, A. S., Kleinberg, W., and Ponder, E. Decreased Red Cell Fragility After Splenectomy, *Am J Physiol* **120** 150, 1937.

75 Gwyn, N. B. Macrocytic Anaemia Associated with Rheumatic Infection, *Canad M A J* **37** 117, 1937.

76 Giordano, A. S., and Blum, L. L. Acute Hemolytic Anemia (Lederer Type), *Am J M Sc* **194** 311, 1937.

77 Massell, B. F., and Jones, T. D. Evaluation of the Signs of Active Rheumatic Fever, with Especial Reference to the Erythrocyte Sedimentation Rate and Leukocyte Count, *New England J Med* **215** 1269, 1936.

in the absence of other known cause, subclinical rheumatic fever should be suspected. Rae ⁷⁸ reemphasized the importance of a high white blood cell count in coronary heart disease. Pearson and Newns ⁷⁹ called attention to an unusual leukocytosis occurring in connection with whooping cough.

The hematologic findings in chronic ulcerative colitis and their relation to prognosis and treatment were studied by Garvin and Bargaen ⁸⁰. They concluded that leukocytosis is uncommon in this disease and that when present it is indicative of some complication. Both the cytoplasmic and the nuclear changes might be used as indexes of the severity and the prognosis of the disease process.

Corwin ⁸¹ observed the cytologic response of the peritoneum of rabbits after injections of Bargaen's vaccine and variable amounts of ricinoleate. An increase in the total number of cells occurred after twelve to twenty-four hours, affecting first the neutrophils and later, within forty-eight hours, the monocytes.

The total white blood cell count not only is of diagnostic and prognostic value in infections but is also an important aid in the study of allergic conditions. Squier and Madison ⁸² stated that eosinophilia and a reduction of the total number of white blood cells followed with equal frequency the ingestion of allergenic foods. They concluded that the simultaneous enumeration of eosinophils and total white blood cells enhances the value of the leukopenic index. Zeller ⁸³ reemphasized the importance of the leukopenic index in the study of allergy and stressed the necessity of counting the white blood cells under identical conditions.

Anemia Associated with Cancer—Anemia may or may not be a complication of cancer. Such anemia may be macrocytic or microcytic. Leukocytosis is usually present. The differential diagnosis between pernicious anemia and carcinoma of the stomach may be difficult when the latter is associated with macrocytic anemia. Held and Goldbloom ⁸⁴

78 Rae, M. V. Coronary Aneurysms with Thrombosis in Rheumatic Carditis, *Arch Path* **24** 369 (Sept.) 1937.

79 Pearson, W. J., and Newns, G. H. Extreme Degree of Leucocytosis in Whooping Cough, *Lancet* **2** 254, 1937.

80 Garvin, R. O., and Bargaen, J. A. Hematologic Picture of Chronic Ulcerative Colitis. Its Relation to Prognosis and Treatment, *Am J M Sc* **193** 744, 1937.

81 Corwin, W. C. Peritoneal Cytologic Response. Experimental Study, *Am J M Sc* **193** 251, 1937.

82 Squier, T. L., and Madison, F. W. Hematologic Response in Food Allergy. Eosinophilia in the Leucopenic Index, *J Allergy* **8** 250, 1937.

83 Zeller, M. Leucopenic Index, *Am J M Sc* **193** 652, 1937.

84 Held, I. W., and Goldbloom, A. A. Carcinoma of Stomach in a Cured Case of Addison-Biermer's (Pernicious) Anemia, *J A M A* **108** 1398 (April 24) 1937.

reported the case of a man with pernicious anemia which was maintained in remission for several years by means of liver therapy. Gastric carcinoma subsequently developed. The authors advised careful studies of the gastrointestinal tract whenever a patient with pernicious anemia relapses while receiving adequate therapy. Because of the apparent relation between achylia, pernicious anemia and gastric carcinoma, Fabian⁸⁵ made quantitative studies of the saliva and reported a reduction in the salivary flow in these three conditions, most marked in pernicious anemia. In his opinion some association exists between the secretory glands of the stomach and the salivary glands. In an effort to differentiate pernicious anemia from the macrocytic anemia of gastric cancer, Lasch⁸⁶ devised a test to determine the amount of intrinsic factor in gastric juice. If the intrinsic factor acts as do other proteolytic enzymes, its presence in gastric contents should be demonstrable by an increase of nonprotein nitrogen in a digestive mixture. Pepsin and trypsin activity were eliminated by incubation at a p_H of 5.5 to 6, which is within the active range of the intrinsic factor. Of 4 patients, 3 with proved gastric carcinoma and 1 in whom it was suspected, 2 showed absence of proteolytic enzyme activity, 1 a decrease and 1 a normal proteolytic reaction. Of 17 persons with pernicious anemia, the enzyme reaction was absent in 12, in 5 it was present in slight degree.

Anemia Associated with Endocrine Dysfunction—In recent years considerable interest has been shown in the relation of the endocrines to hemopoiesis. Reich⁸⁷ offered a complete clinical and experimental summary of this association. In cases of advanced Addison's disease there is usually hypochromic anemia with lymphocytosis. Marked hypochromic anemia may also occur in the multiglandular syndromes. Often lymphocytosis is present in adiposity. After castration of animals there is reduction of the hemoglobin value and red blood cell count with accompanying leukopenia and occasional lymphocytosis. The injection of ovarian extract into castrated females has caused reduction of this lymphocytosis. In eunuchs an increase in monocytes and lymphocytes has been observed. The removal of the thymus produces little if any changes in the peripheral blood of animals, although lymphocytosis is occasionally observed. Extirpation of the parathyroid glands is often followed by increase in the total number of red blood cells. In tetany

85 Fabian, G. Untersuchungen über die Speichelsekretion bei Magencarcinom, perniziöser Anämie und Achylia gastrica, *Ztschr f klin Med* **131** 403, 1937.

86 Lasch, F. Ueber eine biochemische Methode zur quantitativen Bestimmung des "Intrinsic Factor" nach Castle im Magensaft, *Klin Wchnschr* **16** 810, 1937.

87 Reich, C. Endocrines. Their Relation to Blood Disorders, New York State J Med **37** 1271, 1937.

both relative and absolute lymphocytosis have been noted. Similar findings have been observed in acromegaly. In hyperthyroidism the red blood cell count and hemoglobin value usually remain unchanged. The total leukocyte count may be normal or decreased, with accompanying relative lymphocytosis. In severe cases, an absolute increase in the lymphocyte count may occur, the eosinophil count is usually increased. Postoperatively the blood values are usually normal. Similar changes have been observed in colloid goiter. Oral administration of iodides or thyroid usually produces relative lymphocytosis, then injection may cause a temporary increase in the number of platelets, whereas insulin has the opposite effect. In patients with hypothyroidism a reduction of the red blood cell count and hemoglobin value has often been noted, with a color index usually of 1 or more. Hypochromic anemia may occur in hemachromatosis, presumably because of disturbances of iron and pigment metabolism.

Since hypothyroidism is usually associated with decreased hemopoietic activity, Limarzi, Keeton and Seed⁸⁸ induced the condition by thyroidectomy in a patient with polycythaemia vera. They stated that the blood changes were in the direction of normal. There was a perceptible decrease in the total number of red blood cells. Normal values were obtained for the total blood plasma, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Jaffé⁸⁹ discussed the association of hypothyroidism and anemia and concluded that he could not satisfactorily explain the mechanism of the blood changes.

Sharpe⁹⁰ studied a series of 20 patients with myxedema and observed anemia in 9. In 2 cases both pernicious anemia and hypothyroidism were diagnosed. He concluded that achlorhydria may facilitate the development of the anemia of myxedema but that it is not an essential etiologic factor. In his opinion defective hemopoiesis results from sluggish oxidation and can be corrected only by thyroid medication.

Guinea pigs were hypophysectomized by McFarlane and McPhail.⁹¹ No changes were observed in the number of red blood cells or in the hemoglobin value. When solution of posterior pituitary was injected into animals both before and after operation, anemia of varying severity

88 Limarzi, L. R., Keeton, R. W., and Seed, L. Early Effect of Total Thyroidectomy in a Case of Polycythemia Vera (Vaquez-Osler Syndrome), *Proc. Soc. Exper. Biol. & Med.* **36** 353, 1937.

89 Jaffé, R. H. Chronic Thyroiditis, *J. A. M. A.* **108** 105 (Jan 9) 1937.

90 Sharpe, J. C. Anemia of Myxedema. Its Classification and Treatment, *Am. J. M. Sc.* **194** 382, 1937.

91 McFarlane, W. D., and McPhail, M. K. Pituitrin Injections and the Blood Picture in the Normal and Hypophysectomized Guinea Pig, *Am. J. M. Sc.* **193** 385, 1937.

resulted Meyer and his associates⁹² hypophysectomized rats and placed them in an oxygen deficient chamber. Anemia and decrease of reticulocytes below normal invariably occurred after the operation. Unlike the observation for normal rats, exposure to reduced oxygen tension failed to produce reticulocytosis or hyperplasia of the bone marrow. When, however, the stimulus was applied within ten days after the hypophysis was removed, an increase occurred in the red blood cell count and in the hemoglobin value. No changes were observed after a lapse of twenty-five or more days after operation. Splenectomy before removal of the hypophysis did not affect the results. Liver extract was of no value in correcting the anemia. The gonadotropic substance from the urine of pregnant women (antuitrin S) produced reticulocytosis but did not alter the red blood cell count or the hemoglobin value. Thyroxin not only produced reticulocytosis but increased the number of red blood cells and the hemoglobin value. Although in the authors' opinion the pituitary gland probably affects hemopoiesis, it was concluded that there was insufficient proof of direct hormonal action. Flaks, Himmel and Zlotnik,⁹³ on the other hand, said they believed that a hypophysial hormone exerts control over erythropoiesis. Wilson⁹⁴ observed changes in the white blood cells of rabbits after the intravenous injection of a gonadotropic preparation. Leukocytosis usually occurred within five to eight hours and was maintained for forty-eight to seventy-two hours. There was relative and absolute increase of the polymorphonuclear leukocytes, with decrease of the other leukocytic elements. The values gradually returned to normal.

Gilman and Goodman,⁹⁵ in a series of carefully controlled experiments on dogs and rabbits, demonstrated that "pituitrin anemia" might be the result of water retention. The lowered osmotic pressure of the serum presented an abnormal environment for red blood cells and caused their destruction. The authors found that by maintenance of a normal electrolyte concentration in the serum after injections of solution of posterior pituitary, the resulting anemia could be prevented.

Achylia associated with insufficiency of the anterior lobe of the pituitary gland was observed in 5 cases by Snapper.⁹⁶ In 1 case true

92 Meyer, O. O., Stewart, G. E., Thewlis, E. W., and Rusch, H. P. Hypophysis and Hematopoiesis, *Folia haemat* **57** 99, 1937.

93 Flaks, J., Himmel, I., and Zlotnik, A. Sur l'existence d'une hormone hemopoïétique dans l'hypophyse, *Presse med* **45** 1261, 1937.

94 Wilson, D. Effect of Anterior Pituitary-Like Hormone on the Blood Picture in Rabbits, *Endocrinology* **21** 96, 1937.

95 Gilman, A., and Goodman, L. Pituitrin Anemia, *Am J Physiol* **118** 241, 1937.

96 Snapper, I. Relation Between Anterior Pituitary Insufficiency and the Function of the Stomach and Bone Marrow, *Nederl tijdschr v geneesk* **81** 265, 1937.

pernicious anemia developed, and in another anemia associated with a high color index was found. In the 3 remaining cases there was no anemia, but there was evidence of involvement of the central nervous system. It was the author's opinion that there exists a relation between the pituitary gland and the stomach, and as a result of some disturbance of this association, either the hemopoietic or the central nervous system may be affected. Snapper, Groen, Hunter and Witts⁹⁷ said they believed that the pituitary defect occurs first, followed by achlorhydria and later anemia or subacute combined degeneration. They admitted, however, that sufficient proof of this theory is lacking.

IRON DEFICIENCY

Retention, Transportation and Utilization of Iron—During recent years contributions to the knowledge of iron metabolism have come chiefly from animal studies. In contrast to the methods of animal experimentation the present trend of interest is in the direction of investigations on human subjects of the absorption of iron, its mode of transference in the body, its retention and its availability for the formation of hemoglobin. In spite of numerous studies of the intake and excretory balance of iron, there is as yet no agreement as to the minimum amount of dietary iron required by a healthy adult. Excreted iron may never have been absorbed, it may have been absorbed, unused and later excreted or it may be unconserved hemoglobin iron and iron from the breakdown of tissue cells. The iron of various foods cannot be absorbed equally from the digestive tract, and it is not certain that all the metal absorbed is available for physiologic use. It is possible, as Heath and Patek⁹⁸ have done, to calculate the total quantity of iron required by the human body from birth throughout life, but such calculations are based on an assumption of 100 per cent conservation of breakdown iron. In the healthy adult approximately 75 mg of iron is released daily by the disintegration of erythrocytes, if the efficiency of conservation of the metal were 90 per cent, the daily loss to be replaced by diet would be 75 mg. Hemorrhage or an abnormal rate of destruction of the red blood cells would, of course, increase this figure.

Leverton and Roberts⁹⁹ carried out continuous balance studies on 4 healthy young women for from three to five months. The loss of iron

97 Snapper, I, Groen, J, Hunter, D, and Witts, L J. Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, *Quart J Med* **6** 195, 1937.

98 Heath, C W, and Patek, A J, Jr. Anemia of Iron Deficiency, *Medicine* **16** 267, 1937.

99 Leverton, R M, and Roberts, L S. Iron Metabolism of Normal Young Women During Consecutive Menstrual Cycles, *J Nutrition* **13** 65, 1937.

by menstruation was slight, but the calculation of iron requirements gave an optimum daily allowance for a 56 Kg woman of 16 to 17 mg daily

It is now common experience that for optimum regeneration of hemoglobin in patients with anemia much greater amounts of medicinal iron are required than are necessary for the synthesis of hemoglobin, and this is true regardless of the chemical state of the iron administered. The question arises as to whether the excess of iron is needed solely because of inefficient absorption or whether, after absorption only a portion of the metal is put to physiologic use. Recent studies by a number of workers emphasize the discrepancy between retained iron and that employed in the formation of hemoglobin.

Reimann, Fritsch and Schick¹⁰⁰ carried out iron balance experiments on 7 patients with anemia due to iron deficiency and on 2 healthy persons. To all the subjects iron was given, usually ferrous chloride 100 mg daily. They detected no retention of the metal by the healthy subjects but about 50 per cent retention by the patients with anemia. Of the total iron administered to these patients, 20 per cent went into new hemoglobin, and of the iron retained, about 45 per cent was used for hemoglobin synthesis, the difference presumably effecting repletion of the iron stores. These authors concluded that a positive iron balance with retention of iron forms the basis for the therapeutic action of iron. Iron balance studies clearly differentiate anemia due to iron deficiency from other types of anemia.

A series of investigations of the retention and utilization of iron has been reported by Fowler and Barer¹⁰¹. Their earlier work paralleled in scope the studies of Reimann and his colleagues, but their results differed somewhat from those of the German workers. Ten patients with hypochromic anemia were studied during continuous six day periods with respect to the intake and excretion of iron and the formation of new hemoglobin. To each patient was given iron and ammonium citrates, 1 Gm three times a day. They found that of the total iron administered, an average of 32.6 per cent was retained, but only about 2 per cent was used for new hemoglobin. There was no correlation between the retention and the utilization of the orally administered iron, and as much as 5.85 Gm of the metal was retained by 1 patient. They suggested a possible deleterious effect of continued administration of large doses of iron, in that such quantities of retained metal might

100 Reimann, F., Fritsch, F., and Schick, K. Eisenbilanzversuche bei Gesunden und bei Anämischen. II. Untersuchungen über das Wesen der eisenempfindlichen Anämien ("Asiderosen") und der therapeutischen Wirkung des Eisens bei diesen Anämien, *Ztschr f klin Med* **131** 1, 1936.

101 Fowler, W. M., and Barer, A. P. Retention and Utilization of Orally Administered Iron, *Arch Int Med* **59** 561 (April) 1937.

lead to pigmentary cirrhosis of the liver. The discrepancy between their observations of the percentage of iron utilized for new hemoglobin and those reported by the German workers may be attributed to the much smaller doses of iron used by the latter in their studies. This view is supported by a later study of Fowler, Barer and Spielhagen,¹⁰² in which they reported a much higher percentage of iron utilization when smaller doses were administered.

Barer and Fowler¹⁰³ studied the iron exchange of 15 patients with achlorhydria and 11 with normal or low gastric acid values in an attempt to ascertain the effect of gastric acidity on the retention of iron. The subjects were consistently in negative iron balance while receiving diets supplying less than 7 mg of the metal daily. In the presence of achlorhydria there was diminished retention of dietary iron but when medicinal iron was given, 500 mg daily, the percentage of the metal retained was not affected by lack of free hydrochloric acid. The administration of hydrochloric acid to patients with achlorhydria did not increase the retention either of medicinal or of food iron. They also made the striking observation, in direct contrast to the report of Reimann and his colleagues, that the presence of anemia did not in their studies influence the amount of iron retained.

Barer and Fowler¹⁰⁴ investigated, by means of iron balance studies in 10 cases of hypochromic anemia, the effect of copper and liver extract supplements on the retention and utilization of iron. They found that addition of copper led to diminished retention but slightly increased utilization of iron when the latter was given in the relatively small amounts of 217 to 260 mg daily. When 400 to 500 mg was given the effect of copper supplements was negligible. Addition of liver extract was followed by a slightly decreased retention of iron. The rise in hemoglobin in their series was no more rapid with the addition of copper or liver extract than with iron alone.

The same authors¹⁰⁵ reported their experiences with iron administered parenterally. To 4 patients 0.1 Gm of iron and ammonium citrates was given daily by intramuscular injection. The iron was retained but failed to appear in newly formed hemoglobin. From this observation they concluded that parenterally administered iron cannot

102 Fowler, W. M., Barer, A. P., and Spielhagen, C. F. Retention and Utilization of Small Amounts of Orally Administered Iron, *Arch. Int. Med.* **59** 1024 (June) 1937.

103 Barer, A. P., and Fowler, W. M. Influence of Gastric Acidity and Degree of Anemia on Iron Retention, *Arch. Int. Med.* **59** 785 (May) 1937.

104 Barer, A. P., and Fowler, W. M. Influence of Copper and a Liver Fraction on the Retention of Iron, *Arch. Int. Med.* **60** 474 (Sept.) 1937.

105 Fowler, W. M., and Barer, A. P. Retention and Utilization of Parenterally Administered Iron, *Arch. Int. Med.* **60** 967 (Dec.) 1937.

be recovered in newly formed hemoglobin. It is not possible to accept without qualification the results of this study. Although it is difficult to conceive of a situation in which parenteral iron therapy is indicated, the high degree of utilization of injected iron for new hemoglobin has been demonstrated by numerous investigators and is in accord with our own experience. The apparently contradictory results obtained by the workers in Iowa may be due to their use of relatively small doses of iron, 12.3 mg daily, since an optimum rate of increase of hemoglobin utilizes approximately three times this amount.

The retention of orally administered iron by persons with anemia and by those with normal blood values was studied by Brock and Hunter¹⁰⁶. They found that both anemic persons and those with normal blood values retained large amounts of orally administered iron and that the retention was actually much greater than might have been inferred from the rate of increase of hemoglobin. Brock¹⁰⁷ also reported that only 1 of these patients with hypochromic anemia showed an increase in hemoglobin commensurate with the iron retained. Another patient had but slight improvement of anemia, although sufficient iron was retained to have caused the hemoglobin to become normal had utilization of the metal been complete. When the dosage of iron was doubled the hemoglobin value rapidly rose to normal. Evidence was presented in this communication for the greater effectiveness of an excess of iron as compared with a theoretically sufficient amount of iron. Small doses of ferrous salts, such as 0.6 Gm daily, were not advised, since ease of absorption is not the sole factor involved. Brock advanced the supposition that relatively large amounts of iron in the intestine might facilitate the absorption of other minerals and substances necessary for hemopoiesis, perhaps by effecting a change in the bacterial flora.

The observations so far described, as well as others to be mentioned, concerning the quantitative difference between iron retained and that used for new hemoglobin serve as a reminder of earlier work of Starkenstein and Weden¹⁰⁸. A decade ago they concluded that determinations of the iron stored in the liver and spleen give no indication of the true effectiveness of preparations used in the treatment of experimental anemia. They advanced the view that the more rapidly iron is stored in the liver and spleen, the less pharmacodynamic efficacy it possesses, and that active iron circulates throughout the organism for a relatively long time.

106 Brock, J. F., and Hunter, D. Fate of Large Doses of Iron Administered by Mouth, *Quart J Med* **6** 5, 1937.

107 Brock, J. F. Relation Between the Hypochromic Anæmias and Iron Deficiency, *Brit M J* **1** 314, 1937.

108 Starkenstein, E., and Weden, H. Weitere Beiträge zur Pharmakologie und Physiologie des Eisens, *Klin Wchnschr* **7** 1220, 1928.

Studies of iron transportation were reported by Heilmeyer and Plotner¹⁰⁹ Determinations were made of the iron content of the serum after parenteral and after oral administration of the metal The normal basal level of the iron was found to be 0.19 mg per hundred cubic centimeters, increasing to 0.24 mg after the giving of 1 Gm of reduced iron by mouth In hypochromic anemia with achlorhydria no such increase occurred In 1 case of anemia due to subacute hemorrhage the iron content rose from 0.03 to 0.35 mg per hundred cubic centimeters after the ingestion of 220 mg of ferrous iron, only a slight increase followed the intake of the same amount of ferric iron

Moore¹¹⁰ found that the normal range for plasma or serum iron is 0.05 to 0.18 mg per hundred cubic centimeters and that the average for men is slightly higher than that for women Moore, Doan and Arrowsmith¹¹¹ subdivided blood iron into (1) iron in hemoglobin, (2) plasma iron, probably organic, not ionized and so not dialyzable, and (3) "easily split-off" iron, which was first described by Barkan (this is apparently associated with the red blood cells, is split off by dilute acids and bases and is an organic nonhemoglobinous form of iron) Plasma iron appeared to be transport iron, its value increased markedly even for normal persons after a single large oral dose of the metal A temporary increase in the plasma iron content occurred in patients with hypochromic anemia during the period of absorption, but the basal level for such patients remained below that for normal persons until the anemia was wholly corrected The authors failed to confirm Barkan's view of "easily split-off" iron as iron in transport and were unable to define its function

Additional observations on iron metabolism have been made in the field of animal experimentation Hart, Elvehjem and Kohler¹¹² found that commercial liver preparations which are effective in the treatment of pernicious anemia were, apart from their iron and copper content, wholly ineffective in the treatment of nutritional anemia in rats On the other hand, when the amount of dietary protein was either qualitatively

109 Heilmeyer, L., and Plotner, H. Eisenmangelzustände und ihre Behandlung, *Klin Wchnschr* **15** 1669, 1936

110 Moore, C. V. Studies in Iron Transportation and Metabolism. Chemical Methods and Normal Values for Plasma Iron and "Easily Split-Off" Blood Iron, *J Clin Investigation* **16** 613, 1937

111 Moore, C. V., Doan, C. A., and Arrowsmith, W. R. Studies in Iron Transportation and Metabolism. The Mechanism of Iron Transportation and Its Significance in Iron Utilization in Anemic States of Varied Etiology, *J Clin Investigation* **16** 627, 1937

112 Hart, E. B., Elvehjem, C. A., and Kohler, G. O. Does Liver Supply Factors in Addition to Iron and Copper for Hemoglobin Regeneration in Nutritional Anemia? *J Exper Med* **66** 145, 1937

or quantitatively inadequate for growth, the rate of regeneration of hemoglobin was significantly retarded in the case of young rats with nutritional anemia, even though sufficient iron and copper supplements were given¹¹³ Beard and Boggess¹¹⁴ found that in the treatment of the nutritional anemia of the rat the weekly intraperitoneal injection of 2 mg of colloidal iron over a period of four weeks was as effective as the daily oral administration of the same quantity of iron for three weeks They determined the utilization for the formation of hemoglobin of orally administered iron to be 6 per cent in the case of a 42 mg dose, divided over a period of three weeks, and 22 per cent for a 10 mg dose over an equal period, for iron given intraperitoneally the utilization was 28 per cent for 8 mg and 87 per cent for 273 mg over a period of four weeks Supplementing the iron with either copper or manganese had no apparent effect Smith and Otis¹¹⁵ found that regeneration of hemoglobin was more rapid in female than in male rats when they received the same amounts of medicinal or of food iron They attributed the difference as possibly due to greater storage of iron in the females, the iron becoming available for hemoglobin formation when copper supplements are given A sex difference in the rate of regeneration of hemoglobin was not observed after two weeks of iron and copper supplemented feedings Mitchell and Hamilton¹¹⁶ confirmed these observations but attributed the sex difference to a larger intake of the basal diet by the male rats in obedience to their greater growth impulse It has been shown that in the case of anemic rats there is an inverse relation between the amount of milk consumed and the rate of regeneration of hemoglobin

The stomachs were removed from 2 dogs by Fontes Kunlin and Thivolle,¹¹⁷ and the animals were subsequently maintained on a diet of rice and milk During a period of six months progressively severe hypochromic anemia developed, which the authors attributed to achlorhydria resulting from gastrectomy

113 Pearson, P B, Elvehjem, C A, and Hart, E B The Relation of Protein to Hemoglobin Building, *J Biol Chem* **119** 749, 1937

114 Beard, H H, and Boggess, T S Comparison of Oral Administration Versus Intraperitoneal Injection of Colloidal Iron upon Blood Regeneration in Nutritional Anemia of the Rat, *Am J Physiol* **118** 211, 1937

115 Smith, M D, and Otis, L Sex Variations in the Utilization of Iron by Anemic Rats, *Science* **85** 125, 1937

116 Mitchell, H H, and Hamilton, T S Sex Differences in Anemic Rats, *Science* **85** 364, 1937

117 Fontes, G, Kunlin, J, and Thivolle, L L'anémie consecutive a la gastrectomie ne peut être qu'hypochrome, *Nutrition* **6** 331, 1936

Continuing their studies of the role of amino acids in hemoglobin regeneration, Fontes and Thivolle¹¹⁸ reported further observations on dogs made anemic by repeated bleeding in which, presumably, there was depletion not only of iron but of other substances required for hemopoiesis. They reported results gained from the use of a combination of tryptophan, histidine and the globinates of iron, copper and manganese as superior to those obtained from liver. Additional studies of the hypochromic anemia of dogs following gastrectomy were reported by Mettier, Kellogg and Purviance¹¹⁹. Predigested beef was not retained by the animals, and iron and ammonium citrates led to an increase in the total daily output of hemoglobin of from 0.25 to 2.03 Gm. Liver extract by injection was ineffective.

Landsberg¹²⁰ studied the reticulocyte response during induction of acute fatal hookworm infestation in dogs. He found the reticulocytosis accompanying the developing anemia identical with that occurring during induction of anemia by hemorrhage and so concluded that no evidence existed for the theory of myelotoxin inhibition in the etiology of hookworm anemia. He also found no signs of hemolysis in the dogs with hookworm anemia.

Nutritional Anemia of Children—During the past year a number of studies have been reported bearing on the iron requirement during infancy and the treatment of the nutritional anemia of early childhood. Stearns and McKinley¹²¹ studied the iron excretion of 7 infants, commencing at about the tenth day after birth. This is the period of maximum destruction of blood, and they found the lowest blood iron values between the fourth and the sixth week of life. During this period the infants remained in constant negative iron balance, with a daily loss of 1.25 mg. of the metal. They said they believed that a supplementary dietary source of iron is desirable before the sixth month. Studies of iron balance were carried out by Stearns and Stinger¹²² on

118 Fontes, G., and Thivolle, L. Trois nouveaux composés proteido-métalliques. Les globinates de fer, de cuivre et de manganèse, la thérapeutique équilibrée et totale de l'anémie secondaire, valeur comparée du foie de veau cru, Bull. Acad. de med., Paris **116** 314, 1936.

119 Mettier, S. R., Kellogg, F., and Purviance, K. Studies on Hypochromic Anemia in Dogs. The Evaluation of Predigested Beef, Iron and Liver Extract on the Formation of Hemoglobin After Gastrectomy, J. Clin. Investigation **16** 107, 1937.

120 Landsberg, J. W. Reticulocyte Response in Hookworm Anemia, Am. J. Hyg. **26** 60, 1937.

121 Stearns, G., and McKinley, J. B. Conservation of Blood Iron During the Period of Physiological Hemoglobin Destruction in Early Infancy, J. Nutrition **13** 143, 1937.

122 Stearns, G., and Stinger, D. Iron Retention in Infancy, J. Nutrition **13** 127, 1937.

14 healthy infants aged 7 to 54 weeks. One subject received human milk and was never in negative balance, although the amount of iron retained was small. The others were given evaporated cow's milk with various modifications of the formula. All the infants receiving cow's milk were in negative balance and lost an average of 0.05 mg of iron daily. There was no relation between the age of the infant and the ability to retain iron. Egg yolk and spinach supplements did not increase the retention of iron. Retention was, however, markedly increased by the giving of a special iron-containing cereal or iron and ammonium citrates. There was no apparent relation between the amount of iron retained and the intake of potassium, calcium or phosphorus. They concluded that a daily intake of approximately 0.5 mg of iron per kilogram, either as food iron or as a soluble salt, is necessary to insure retention of the metal and that ample retention is secured by a daily intake of 1 to 1.5 mg per kilogram.

Schlutz, Morse and Oldham¹²³ determined the iron retention and utilization of 3 anemic infants. They found that additional iron supplied by pureed spinach was not retained by these infants, the iron of apricots, although retained to a slight extent, effected no change in the hemoglobin level. One hundred milligrams of the metal, supplied either as ferrous sulfate or as iron and ammonium citrates, led to a marked increase in the retention of iron and a rise in the hemoglobin value. The ferrous form was no more efficacious than the ferric salt. Supplementary copper, given as copper sulfate, had no effect either on iron retention or on the hemoglobin level. The iron exchange of 4 children with normal blood values and 2 with anemia was studied by Hutchison.¹²⁴ The children ranged in age from infancy to 11 years. Four day preliminary control periods were used, followed by consecutive seven day test periods. During the test periods there was wide variation in the excretion of iron, in spite of a constant intake. Ferrous sulfate was given in amounts totaling 4 to 8 Gm weekly, supplying 0.803 to 1.607 Gm of iron. Over variable lengths of time up to 112 days the subjects retained large amounts of iron, in some cases from three to seven times the normal total body content of the metal. In the case of the anemic children, less than 10 per cent of the retained iron was recoverable as new hemoglobin. For these children the retention of iron was not demonstrably allied with the ability to secrete hydrochloric acid. Hutchison suggested that retained iron stored in the liver cannot be used for the formation of hemoglobin and that, consequently, large

123 Schlutz, F. W., Morse, M., and Oldham, H. Effect of Various Supplements to the Diet on the Iron Balance of the Anemic Infant, *J. Pediat.* **10** 147, 1937.

124 Hutchison, J. H. Studies on the Retention of Iron in Childhood, *Arch. Dis. Childhood* **12** 305, 1937.

doses of medicinal iron are necessary since only iron which overflows from the liver into the circulation can be utilized for hemoglobin synthesis. The gastric acidity of infants and young children was studied by Stewart¹²⁵. Four groups were employed (1) anemic subjects, (2) postanemic subjects, (3) those with other illnesses and (4) healthy children. The amount of acid secreted by the stomach was determined in response to a stimulus of 40 cc of 7 per cent alcohol. The author found no correlation between the incidence of anemia and the degree of gastric acidity. She concluded that in the cases studied, anemia was caused solely by deficiency of nutritional iron and that achlorhydria is more likely to follow anemia than to precede it. She did, however, suggest that chronic gastritis might lead to achlorhydria and that the two conditions might together influence adversely the absorption of iron. Fullerton,¹²⁶ continuing his studies of the blood values for the poorer persons of Aberdeen, determined the hemoglobin level of 789 infants of all ages up to 23 months. His findings indicated that the iron content at birth is of great importance in determining the time of onset of anemia due to iron deficiency. However, the amount of storage iron was related primarily to the birth weight, and no significant correlation was found between the common degrees of maternal iron deficiency and the incidence of anemia in infancy. It was found that breast-fed infants were less liable to anemia than those receiving an artificial diet. Infections produced a rapid fall in the hemoglobin values of the infants studied, and even after subsidence of such infection there might be inhibition of response to treatment for a long time. In a series of 298 infants examined by Fullerton, subnormal hemoglobin levels, less than 11 Gm per hundred cubic centimeters, were found for 87 per cent.

Elvehjem, Duckles and Mendenhall¹²⁷ concluded from the treatment of 70 anemic infants and children of preschool age that iron and copper, a combination of 0.2 Gm of ferric pyrophosphate (supplying 0.025 Gm of iron) and 0.004 Gm of copper sulfate (supplying 0.001 Gm of copper daily), caused maximum regeneration of hemoglobin with results superior to those gained from the use of the iron salt alone. Kato¹²⁸ carried out experimental and clinical studies of the effect of an iron and cobalt mixture in the treatment of nutritional anemia. To anemic

125 Stewart, A. Gastric Acidity in Infants and Young Children Under Normal and Pathological Conditions, with Special Reference to Nutritional Anaemia, *Brit J Child Dis* **34** 1, 1937.

126 Fullerton, H. W. The Iron-Deficiency Anaemia of Late Infancy, *Arch Dis Childhood* **12** 91, 1937.

127 Elvehjem, C. A., Duckles, D., and Mendenhall, D. R. Iron Versus Iron and Copper in the Treatment of Anemia in Infants, *Am J Dis Child* **53** 785 (March) 1937.

128 Kato, K. Iron-Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, *J Pediatr* **11** 385, 1937.

infants he gave 0.5 Gm of iron and ammonium citrates daily, later supplemented with 0.025 to 0.05 Gm of cobalt daily. He concluded that the action of cobalt is probably catalytic, but the evidence presented of its actually enhancing the effect of iron in the series reported is not wholly convincing.

Mackay and Jacob¹²⁹ recommended the use of a stable solution of ferrous sulfate in the treatment of nutritional anemia of young children. Stability was increased by the addition of hypophosphorous acid to a solution of ferrous sulfate with dextrose. The dosage should be such as to supply 0.3 to 0.6 Gm of the iron salt daily.

Ferrous chloride has been prepared in relatively stable form by dissolving it in a solution of cevitamic acid, thereby protecting it from oxidation for about three months. Glanzmann¹³⁰ and Stolleis¹³¹ reported the efficacious use of this preparation in the treatment of a variety of anemias of early childhood. The former obtained excellent results from the use of liver, ferrous sulfate and cevitamic acid in the treatment of 1 patient with celiac disease and anemia. He concluded that the combination of ferrous iron and vitamin C is preferable to iron alone and suggested that vitamin C is related to iron metabolism in a manner analogous to the role of vitamin D in the metabolism of calcium and phosphorus.

The prophylactic value of iron therapy in infancy was emphasized by Alpert¹³². He concluded after a survey of the literature that "the role of copper, if any, is still unsettled, and that a longer period of observation and clinical trial is needed to determine whether copper is an important element in the treatment of anemia."

In the treatment of anemia due to iron deficiency, the use of copper in conjunction with iron has been repeatedly advocated in spite of the fact that earlier clinical studies which tended to demonstrate its value have, in general, been unconfirmed by subsequent investigations. Our own experience fails to substantiate the value of copper in the treatment of either the nutritional anemia of children or the hypochromic anemia of adults. In the opinion of Hahn,¹³³ the influence of copper

129 Mackay, H. M. M., and Jacob, L. E. A Stable Ferrous Sulphate Mixture for the Treatment of Nutritional Anaemia in Young Children, *Lancet* **2** 570, 1937.

130 Glanzmann, E. Zur Behandlung der Kinderanämien mit askorbinsäurem Eisen, *Schweiz. med. Wchnschr.* **67** 436, 1937.

131 Stolleis, D. Beitrag zur Eisenbehandlung der Anämie in Säuglings und Kindesalter, *Deutsche med. Wchnschr.* **63** 819, 1937.

132 Alpert, G. R. Physiological and Nutritional Anemias of Infancy, *Arch. Pediat.* **54** 268, 1937.

133 Hahn, P. F. Metabolism of Iron, *Medicine* **16** 249, 1937.

on iron metabolism has been greatly overemphasized. He stated that from a practical point of view there is no indication for the inclusion of this element in anemia therapy.

Hypochromic Anemia of Adults—There has been a revival of interest in chlorosis, a disease which has been almost forgotten or which when mentioned has been regarded as a nonspecific anemia of adolescent girls caused by excessive menstrual loss of blood and probably dependent on endocrine imbalance. Olef¹³⁴ attributed the apparent remarkable decrease in the incidence of chlorosis to three factors: (1) more accurate diagnostic methods by means of which many conditions formerly classified as chlorosis could now be proved to be pulmonary tuberculosis, bleeding from the digestive tract or, in spite of pallor, conditions associated with normal hemoglobin values, (2) improvement in general and personal hygiene, and (3) the present tendency to place conditions formerly called chlorosis in other etiologic categories. He reported 3 cases of chlorosis, 2 of them occurring in twins. The characteristics of this disorder, according to Olef, which together distinguish it from other anemias of young women, are the high incidence of gastric hypoacidity and achlorhydria, the frequent reduction of the plasma protein value without reversal of the albumin-globulin ratio, small, unusually flat red blood cells that are poor in hemoglobin and the common finding of thrombocytosis, which may be marked. Heath¹³⁵ reported 2 cases of chlorosis. He attributed the disorder to one or more abnormal factors at puberty, such as unusually rapid growth, excessive menstruation, poor dietary intake of iron and such gastrointestinal disorders as achlorhydria and prolonged diarrhea.

Schiødt¹³⁶ studied the rate of regeneration of red blood cells of 50 patients with hematemesis or melena from peptic ulcer. The patients received the Meulengracht treatment, a full diet of strained food from the first day of admission to the hospital. To exclude, so far as possible, the effects of prolonged bleeding on the determinations of the regeneration rate, the lowest blood value after admission of the patient to the hospital was taken as a starting point. The individual erythrocyte curves were remarkably straight, and all tended to meet at one point, 4,540,000 red blood cells per cubic millimeter thirty-three days after the lowest count was obtained, regardless of the starting level.

134 Olef, I. Chlorosis, *Ann Int Med* **10** 1654, 1937.

135 Heath, C. W. Iron Deficiency in Girls. Chlorosis, *M Clin North America* **21** 389, 1937.

136 Schiødt, E. Observations on Blood Regeneration in Man. I. The Rise in Erythrocytes in Patients with Hematemesis or Melena from Peptic Ulcer, *Am J M Sc* **193** 313, 1937.

These observations were in conformity with the author's theory of the normal rate of exchange which is expressed by the equation

$$\text{Average daily rise} \times \text{Longevity of erythrocytes} = \text{Normal value} - \text{Lowest value}$$

Substituting values actually determined in this equation and using 4,540,000 for the normal value, the average span of life of the erythrocytes was found to be thirty-three days. Since the end point of regeneration of the subjects studied was below the accepted normal level, it may be inferred that a check took place. Such a check to the increase of erythrocytes may be explained by a decrease of production, a shortening of life of the red blood cells or an increase of destruction. The size of the check can be assumed to be about 15 per cent of the normal rate of exchange. In a subsequent article Schjødt¹³⁷ reported that age, sex and the form of hemorrhage do not affect greatly the rate of regeneration of erythrocytes. Blood transfusion altered the blood level temporarily but did not hasten regeneration. Additional evidence was presented of the superiority of the Meulengracht treatment for peptic ulcer with hemorrhage.

Idiopathic hypochromic anemia was defined by Fowler and Barer¹³⁸ as, in most cases, a chronic hemorrhagic anemia due to menstrual loss of blood and an improper absorption of iron resulting from deficient gastric secretion. In their cases no evidence was found of faulty iron metabolism. They observed that massive doses of iron produced a more rapid hemoglobin response in hypochromic anemia than is obtained when smaller amounts are employed. However, a daily dose of 1 to 3 Gm of iron and ammonium citrates produced satisfactory results in their cases, even in the presence of achlorhydria, and led to storage of iron as well as the formation of hemoglobin. Iron by intramuscular injection was practically without effect. The syndrome of hypochromic anemia, achlorhydria and atrophic gastritis was described by Morrison, Swalm and Jackson¹³⁹. They reported on 11 patients with anemia with a low color index, 9 of these showed complete achlorhydria after histamine stimulation and 2 had marked hypochlorhydria. Gastrosopic studies of these patients revealed various degrees of atrophic gastritis. The authors concluded that the anemia was a manifestation of a gen-

137 Schjødt, E. Observations on Blood Regeneration in Man. II. The Influence of Sex, Age, Form of Hemorrhage, Treatment and Complications on Erythrocyte Regeneration After Hematemesis and Melena from Peptic Ulcer, *Am J M Sc* **193** 327, 1937.

138 Fowler, W. M., and Barer, A. P. Etiology and Treatment of Idiopathic Hypochromic Anemia, *Am J M Sc* **194** 625, 1937.

139 Morrison, L. M., Swalm, W. A., and Jackson, C. L. Syndrome of Hypochromic Anemia, Achlorhydria and Atrophic Gastritis, *J A M A* **109** 108 (July 10) 1937.

eralized metabolic disorder in which atrophic gastritis played a dominating role and that absent or low free gastric acid was an important pathogenic factor

Merklen and his associates¹⁴⁰ and later Manizade⁵⁹ studied the incidence of anemia following partial gastric resection for ulcer. Observations on the blood were made after varying intervals up to twelve years after operation. The former group of investigators found normal blood values in the majority of their series of 28 cases. When anemia occurred it was of mild degree and of hypochromic type. Manizade observed normal erythrocyte and hemoglobin values for 36 of 40 patients studied. The 10 per cent incidence of anemia following partial gastrectomy was attributed to secondary digestive disturbances and to possible constitutional predisposition to anemia.

The treatment of hypochromic anemia was investigated by Gram,¹⁴¹ who calculated the response to therapy as the percentage of the deficit of hemoglobin gained during a ten day period. Thus if the normal value were assumed to be 14 Gm of hemoglobin per hundred cubic centimeters, a patient with 7 Gm would have a 50 per cent deficit, and if after ten days of treatment the hemoglobin value rose to 9 Gm, the percentage of the deficit recovered would be 28.6 per cent. This figure represented Gram's measure of therapeutic response. For optimal results he advised the use of ferrous preparations, supplying 0.3 Gm of iron daily. His patients were treated, for the most part, with ferrous tartrate, 0.5 Gm three times a day. Duckles, Wills and Elvehjem¹⁴² studied the comparative value of iron alone and iron supplemented with copper in the treatment of mild anemia of college women. Iron was given as ferric pyrophosphate, supplying 25 mg of the metal daily, copper as copper sulfate, yielding 1 mg of copper daily. The addition of copper to iron failed to give superior results. Several iron compounds in common therapeutic use were found by Underwood¹⁴³ to contain appreciable cobalt contamination. He suggested that cobalt may possess therapeutic value and may so explain the need for massive doses of iron in the treatment of some patients with hypochromic anemia. An analogy was drawn with the New Zealand "bush-sickness" of sheep, in which there is evidence of cobalt deficiency.

140 Merklen, P., Israel, L., Froehlich, F., and Jacob, A. *Le sang des gastrectomisés*, *Nutrition* **6** 337, 1936.

141 Gram, H. C. *Investigations on the Iron Treatment of Simple Anemias with Control*, *Acta med. Scandinav.*, 1936, supp. 78, p. 207.

142 Duckles, D., Wills, L., and Elvehjem, C. A. *The Treatment of Hypochromic Anemia in College Women*, *J. Am. Dietet. A.* **12** 537, 1937.

143 Underwood, E. J. *Cobalt Content of Iron Compounds and Its Possible Relation to the Treatment of Anemia*, *Proc. Soc. Exper. Biol. & Med.* **36** 296, 1937.

A comprehensive resume of the entire subject of anemia due to iron deficiency, including a series of case reports, was published by Heath and Patek⁹⁸

ANEMIA OF PREGNANCY

Few significant contributions to the literature on anemia of pregnancy have appeared during the past year. A review of the subject was published by Evans,¹⁴⁴ who suggested the following classification of such anemia

I Deficiency anemias of pregnancy

(a) Microcytic

- 1 With normal or only temporary deficiency of gastric secretion
- 2 With permanent deficiency of gastric secretion

(b) Macrocytic

- 1 With normal or only temporary deficiency of gastric secretion
- 2 With permanent deficiency of gastric secretion

II Anemia due to hemorrhage

III Anemia due to sepsis

IV Hemolytic anemia (due to the action of a hemolytic agent of unknown origin)

It may be appropriate to supplement Evans' classification by pointing out that the deficiency operating in microcytic anemia of pregnancy is primarily a lack of iron and that iron deficiency may occur in pregnancy with hypochromia but without microcytosis. Anemia of pregnancy with macrocytic deficiency may result from a lack of Castle's intrinsic or extrinsic factors, from insufficient vitamin B complex, from impairment of intestinal absorption or from inadequate intake of protein. The macrocytic anemia associated with hepatic damage, although due to defective blood formation, can hardly be said to result from deficiency, in the usual sense of the word.

The possible influence of vitamin B deficiency in causing macrocytic anemia during pregnancy was investigated by Elsom.⁵⁴ Eleven pregnant women were divided into two groups. To those in group 1 comprising 8 subjects, a diet was given which possessed the relatively low vitamin B per caloric ratio of approximately 1.66. The vitamin B requirement of the subjects, calculated according to Cowgill's formula, averaged 1.5 at the beginning of the study. The vitamin B demand increased in proportion to the gain in weight of the subjects, and since the diet was both qualitatively and quantitatively constant, the require-

¹⁴⁴ Evans, E. H. Anemias of Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **44** 417, 1937

ment of vitamin B exceeded the supply after about the two hundred and forty-fifth day of pregnancy. Those in group 2 received a varied diet, providing a vitamin B ratio of about 2.8. After the theoretic demand for vitamin B had exceeded the supply, the members of the first group showed clinical signs of vitamin B deficiency, including anorexia, constipation, glossitis with ulceration of the tongue, paresthesia of the extremities, impairment or loss of vibratory sense and symptoms of anemia. Studies of the blood for this group revealed macrocytic anemia, with a high color index, poikilocytosis and immature erythrocytes and leukocytes. Similar changes in the blood were not observed for the control group.

The subjects with evidence of vitamin B deficiency were given yeast by mouth or liver extract parenterally, with complete relief of all symptoms and with return to normal of the blood findings.

Napier and Das Gupta¹⁴⁵ carried out studies of the blood of women in India during pregnancy. He found the hemoglobin level of females in the general coolie population to be considerably below that of females of other countries, but there was no evidence of a general lowering of the hemoglobin value during pregnancy. The incidence of outspoken anemia was slightly greater during gestation, especially for the younger women and during the first pregnancy.

Mays¹⁴⁶ reported a case of severe macrocytic anemia of pregnancy that was of special interest because of associated marked thrombopenia with purpuric manifestations. The anemia, thrombopenia and purpura responded favorably to parenteral liver therapy. Malarial parasites were found in the blood of this patient, but the response to liver occurred independently of treatment of the malaria.

POLYCYTHEMIA

Lee¹⁴⁷ emphasizes the familial element in polycythaemia vera. He said he felt that gradations of severity of the disease in certain families is against the idea of a neoplastic cause but favors a secondary response to some substance or condition, which, however, is not a recognizable form of anoxemia. Lee said he favored phenylhydrazine rather than venesection or roentgen therapy, because of its easier application to the average ambulatory patient.

145 Napier, L. E., and Das Gupta, C. R. Haematological Studies in the Indians. VII. The Incidence and Degree of Anaemia Amongst Pregnant Females of the Coolie Population, *Indian J. M. Research* **24** 1159, 1937.

146 Mays, C. R. Anemias of Pregnancy. A Review and Report of a Case of the Macrocytic Type with Purpuric Manifestations and Malaria, *South Surgeon* **6** 458, 1937.

147 Lee, R. I. A Case of Polycythemia Vera or Erythremia, *M. Clin. North America* **21** 369, 1937.

Mogensen¹⁴⁸ found that five months' treatment with gastric lavage as well as the low animal protein diet of Herzog was ineffective in producing a remission in a patient with a red blood cell count of 10,000,000 per cubic millimeter

Bernard¹⁴⁹ was able to produce irritation of the bone marrow by the injection of tal into the marrow. Leukemic and polycythemic reactions developed

In a man of 66 years with Geisbock's type of polycythemia, Decourt, Mathieu and Blaire¹⁵⁰ found that irradiation over the hypophyseal area was ineffective. However, in seven months fifty-three irradiations over the bones and seven over the spleen caused a reduction in the red blood cell count from 9,200,000 to 5,800,000 per cubic millimeter. Apropos of this case, Lechelle¹⁵¹ commented on a 24 year old woman with a hypophyseal adenoma, polycythemia and acromegaly. Removal of the adenoma was followed by amelioration of the condition, suggesting a connection between the two. Decourt, Joly and Blain¹⁵² obtained good results with teleroentgenotherapy in a woman of 54 years. After six months the red blood cell count was reduced from 7,350,000 to 4,000,000 per cubic millimeter. In the authors' opinion, the irradiation does not cause lysis or necrosis of the cells but hastens maturation and death from senility.

Lemierre, Laporte, Reilly and Laplane¹⁵³ reported the development of polycythemia (8,000,000 cells) in a 39 year old man with infection due to *Bacillus perfringens* of the perinectal fossa. The symptoms included icterus and nephritic complications, conditions in which one frequently finds anemia.

Josland¹⁵⁴ found that the addition of 1 per cent cobalt sulfate to the diet of 2 rats was followed by loss of weight and polycythemia

148 Mogensen, E. Polycythemia Vera. Hypothesis Concerning Its Gastro-genic Pathogenesis Together with a Case in Which Treatment Consisted of Gastric Lavage and Diet, *Hospitalstid* **80** 1271, 1937

149 Bernard, J. Polyglobulies et leucemies provoques par les injections intra-medullaires de goudron, *Ann de med* **40** 373, 1936

150 Decourt, J., Mathieu, P., and Blaire, G. Erythremie du type Geisbock. Echec de la radiotherapie de la region infundibulo-hypophysaire, remission sous l'influence de la radiotherapie osseuse et splenique, *Bull et mem Soc med d hop de Paris* **53** 807, 1937

151 Lechelle, P. Polyglobulies d'origine centrale et erythremies du type Geisbock, *Bull et mem Soc med d hop de Paris* **53** 978, 1937

152 Decourt, J., Joly, M., and Blaire, G. Maladie de Vaquez, traitee avec succes par la teleroentgentherapie totale, *Bull et mem Soc med d hop de Paris* **53** 812, 1937

153 Lemierre, A., Laporte, A., Reilly, J., and Laplane, R. Sur un cas d'erythremie apparue au cours d'une infection prolongee a "*Bacillus perfringens*," *Bull et mem Soc med d hôp de Paris* **53** 831, 1937

154 Josland, S. W. The Effect of Feeding Cobalt to Rats, *New Zealand J. Scient. Tech* **18** 474, 1936

within seven weeks. There was no cirrhosis of the liver, although much of the cobalt was stored in this organ.

Brewer¹⁵⁵ was not able to produce cobalt polycythemia in dogs, even with comparable doses which would have caused a 50 per cent increase in red blood cells in the rat. Cobalt chloride caused toxic necrosis of the tissues of the dog on subcutaneous injection, although this method of administration is not injurious to the rat. Davis,¹⁵⁶ however, found that the oral administration of 2 mg of cobalt (as cobalt chloride) per kilogram daily to dogs produced about a 20 per cent increase in the erythrocyte value. No toxic symptoms were noted in dogs which received 6 mg per kilogram daily for three weeks.

Cohen¹⁵⁷ found that the characteristic change in the fundus in polycythemia is distention and engorgement of the retinal veins, due to increase in blood volume and thinness of the venous wall. A purplish color is caused by an increase in carbon dioxide. Individual patients may show venous engorgement, edema of the disks, retinal hemorrhages, postneuritic atrophy of the optic nerve and perivascular transudation of plasma.

Vascular complications were noted in one third of the patients with polycythemia by Norman and Allen,¹⁵⁸ a greater incidence than that in other patients of the same age and sex. Treatment of polycythemia is advisable to prevent vascular lesions.

In the patient reported on by Schnetz¹⁵⁹ thromboarteritis pulmonalis developed. Clinical symptoms of acute aleukemic myelosis (agranulocytosis) were noted. In another patient with polycythemia a phlegmon of the hand developed, accompanied by mild neutropenia. Improvement was noted on administration of vitamins A and C.

Seggel,¹⁶⁰ in describing a case of polycythemia, noted the association of hepatic cirrhosis with polyglobulism. Ascites may suggest this lesion or thrombosis of the portal vein. In such cases the patients may also show icterus.

In a 25 year old man with alcoholic cirrhosis of the liver and ascites, polycythemia was present. There was erythrosis, absence of macro-

155 Brewer, G. Erythrocyte Reaction of the Dog to Cobalt, *Am J Physiol* **118** 207, 1937.

156 Davis, J. E. Cobalt Polycythemia in the Dog, *Proc Soc Exper Biol & Med* **37** 96, 1937.

157 Cohen, M. Lesions of Fundus in Polycythemia. Report of Cases, *Arch Ophth* **17** 811 (May) 1937.

158 Norman, I. L., and Allen, E. V. Vascular Complications of Polycythemia, *Am Heart J* **13** 257, 1937.

159 Schnetz, H. Polycythaemia vera mit Ausgang in Agranulocytose und Thromboarteritis pulmonalis, *Folia haemat* **57** 110 1937.

160 Seggel, K. A. Ueber besondere Verlaufsformen der Polycythaemia vera, *Ztschr f klin Med* **132** 466, 1937.

cytosis and characteristics of Vaquez' disease. Relief was obtained with phenylhydrazine, and Benhamou, Foures and Mutin¹⁶¹ concluded that cirrhosis of the liver is not a contraindication to this type of therapy.

From porphyrin studies, Dobriner¹⁶² concluded that there is increased hemopoietic activity in pernicious anemia, polycythaemia vera and Hodgkin's disease.

In none of 6 patients with polycythaemia vera were Israel and Mendell¹⁶³ able to demonstrate gonadotropic substance in the urine (Zondek method).

Sachs, Levine and Griffith¹⁶⁴ studied the reciprocal relation of copper and iron in the blood. The iron content of the blood for normal men was found to average 50 mg per hundred cubic centimeters and for women 45 mg. The copper content of the blood of both was 0.132 mg per hundred cubic centimeters. Hypercupremia was associated with hypoferronemia. In a 65 year old woman with polycythemia, the iron and copper contents of the blood were 53.16 and 0.113 mg, respectively, when the red blood cell count was 6,080,000 per cubic millimeter. On the production of anemia with phenylhydrazine (3,520,000 erythrocytes) the copper and iron contents of the blood were 39.36 and 0.2 mg, respectively. Through relapses and induced remissions the iron content paralleled the red blood cell count, while the copper content rose and fell in a reciprocal relation.

McCance and Widdowson¹⁶⁵ found that less than 0.5 per cent of the iron liberated by the hemolysis of the red blood cells in the acetylphenylhydrazine treatment of a patient with polycythemia was excreted. Of the nitrogen, 31 per cent was eliminated, of the potassium, 5 per cent, and of the copper, 30 per cent. After discontinuance of the medication a rapid destruction of the red blood cells followed, with a temporary rise in the blood urea content to 145 mg per hundred cubic centimeters and with an increased excretion of urea, creatine and undetermined nitrogen.

161 Benhamou, E., Foures, and Mutin, L. Cirrhose de foie avec polyglobulie traitée par la phenylhydrazine, *Sang* **11** 772, 1937.

162 Dobriner, K. Porphyrin Excretion in Feces in Normal and Pathological Conditions, *J Biol Chem* **120** 115, 1937.

163 Israel, S. L., and Mendell, T. H. Excretion of Gonadotropic Substance in Polycythemia Vera, *Endocrinology* **21** 123, 1937.

164 Sachs, A., Levine, V. E., and Griffith, W. O. Reciprocal Relationship of Copper and Iron in the Blood. Polycythemia Vera, *Proc Soc Exper Biol & Med* **35** 6, 1936.

165 McCance, R. A., and Widdowson, E. M. The Fate of Elements Removed from Blood Stream During the Treatment of Polycythaemia by Acetylphenylhydrazine, *Quart J Med* **6** 277, 1937.

Sgalitzer¹⁶⁶ advised the use of "total irradiation" in the treatment of polycythemia. The entire body is irradiated from a source at 15 meters (180 to 200 kilovolts on six successive days for fifteen minutes daily, alternating the ventral and the dorsal surface of the body). The leukocyte number is used as a gauge of treatment. From twelve to twenty-two irradiations may be given in from four to ten weeks, depending on the sensitivity of the leukocytes. Relapses have been noted in from eighteen months to five years.

Bétroux and Marcoulidès¹⁶⁷ found that their patient with erythremia resisted roentgen therapy, in fact, the treatment exaggerated the symptoms. Phenylhydrazine hydrochloride, in doses of 0.05 Gm for four days, 0.1 Gm for four days and 0.15 Gm for three days, gave a satisfactory hemopoietic response.

Limarzi, Keeton and Seed⁸⁸ removed the thyroid gland from a patient with polycythemia. During the course of the subsequent year there was gradual symptomatic and hemopoietic improvement.

Stephens and Kaltreider¹⁶⁸ studied the therapeutic use of venesection in 5 cases of polycythemia. Remissions of from eight months to two years were obtained by withdrawing 500 cc of blood at intervals of one to three days until the red blood cell count, hemoglobin value and hematocrit percentage reached normal or slightly subnormal levels. Excellent symptomatic remissions were experienced, and no evidence of stimulation of the bone marrow (reticulocytosis) was noted.

PURPURA HAEMORRHAGICA

Purpura may be caused by many factors, and various forms have been classified. In an attempt to clarify the complex problems associated with the multiple etiologic factors of purpura, Ainsworth¹⁶⁹ and Mettier and Purviance¹⁷⁰ have offered simple classifications. Peck, Rosenthal and Erf¹⁷¹ have studied the mechanism of the production of

166 Sgalitzer, M. Ueber Röntgen-Totalbestrahlungen bei Blutkrankheiten, *Wien klin Wchnschr* **50** 125, 1937.

167 Bétroux, L., and Marcoulidès, J. Erythémie essentielle (maladie de Vaquez), peu influencée par la téléroentgentherapie totale, rapidement améliorée par le chlorhydrate de phénylhydrazine, *Bull et mém Soc méd d hôp de Paris* **52** 1390, 1936.

168 Stephens, D. J., and Kaltreider, N. L. The Therapeutic Use of Venesection in Polycythemia, *Ann Int Med* **10** 1565, 1937.

169 Ainsworth, M. L. *Purpuras*, Ohio State M. J. **33** 849, 1937.

170 Mettier, S. R., and Purviance, K. Classification and Treatment of the Hemorrhagic States. Value of Roentgen Irradiation of Spleen in Essential Thrombocytopenic Purpura Haemorrhagica, *J. A. M. A.* **108** 83 (Jan 9) 1937.

171 Peck, S. M., Rosenthal, N., and Erf, L. Purpura. Classification and Treatment, with Special Reference to Treatment with Snake Venom, *Arch Dermat & Syph* **35** 831 (May) 1937.

purpura and have classified the disease from a dermatologic and hematologic standpoint. According to these authors, bleeding may be due to diapedesis or to rupture of the capillary wall. Increased capillary pressure, suction and reduction of intercellular tissue between the endothelial cells aid diapedesis. Rhexis of the capillary wall is caused by toxins, heavy metals, snake venom or trauma. In addition to changes in the vessels, purpura may be due to thrombopenia, essential or secondary. To determine which of these factors is the cause of purpura, Peck and his co-workers recommended the snake venom test.

Fleischhacker,¹⁷² studying the pathogenesis of the purpuras associated with deficiency of platelets, observed that the problem could be simplified by studies of the bone marrow. The physicochemical changes of the blood associated with experimental purpura were noted by Tocantins.¹⁷³ He stated that there are a moderate decrease in the viscosity of the blood and a transient increase in the nonprotein nitrogen content. Venous pressure, the viscosity of the plasma, the specific colloid osmotic pressure and the protein content of the plasma are not altered.

Both hereditary and acquired thrombopenic purpura have been described. Posner¹⁷⁴ pointed out that purpura is rare in pregnancy and that even more rare is the occurrence of purpura in the fetus. Wintrobe and Hanrahan¹⁷⁵ concluded from their observations in a series of 62 cases that the disease is predominant in childhood or adolescence, the sex incidence is equal and the disease rarely occurs in Negroes. They added that the course is variable, acute episodes are the rule rather than the exception, and recurrences are common. Pernokis¹⁷⁶ reported 17 cases of symptomatic purpura and 5 cases of idiopathic purpura in a series of 2,728 cases. Purpura associated with dysmenorrhea has been noted by Smith.¹⁷⁷ Hazel and Snow¹⁷⁸ observed purpura in a patient with septicemia due to gonococcal infection. The

172 Fleischhacker, H. Ueber Thrombopenien (Einteilung und Knochenmarksbefunde), *Wien klin Wchnschr* **50** 1480, 1937.

173 Tocantins, L. Physicochemical Changes of the Blood in Experimental Thrombopenic Purpura, *Proc Soc Exper Biol & Med* **36** 402, 1937.

174 Posner, A. C. Purpura Hemorrhagica Complicating Puerperium, *Am J Obst & Gynec* **34** 155, 1937.

175 Wintrobe, M. M., Hanrahan, E. M., Jr., and Thomas, C. B. Purpura Haemorrhagica, *J A M A* **109** 1170 (Oct 9) 1937.

176 Pernokis, E. W. Blood Studies. Report of 2,728 Cases, *J A M A* **108** 1686 (May 15) 1937.

177 Smith, E. C. Menstrual Purpura, *New Orleans M & S J* **90** 214, 1937.

178 Hazel, O. G., and Snow, W. B. Gonococcal Septicemia with Purpura and Arthritis Successfully Treated by Hyperthermia, *J A M A* **109** 1275 (Oct 16) 1937.

relation of purpura and lupus erythematosus was discussed by Keil,¹⁷⁹ who pointed out that the reduction in platelets is due to their withdrawal from the blood stream and their inclusion in the thrombi in the smaller blood vessels. Purpura due to "drug poisoning" has been observed by Kramer,¹⁸⁰ van Andel and Groen,¹⁸¹ Schonberg,¹⁸² Goodman and Levy¹⁸³ and Padget and Moore¹⁸⁴.

Purpura associated with alterations in the permeability of the vascular membranes may be the result of allergy. Wright and Bacal¹⁸⁵ reported a case of allergic tuberculous purpura. Idiopathic thrombopenic purpura due to an anaphylactoid reaction was observed by Lytle and Ward¹⁸⁶. Squier and Madison¹⁸⁷ stressed the importance of food allergy as a cause of purpura and reported 3 cases in which the etiology was proved. That allergic purpura may present a serious surgical problem was stressed by Althausen and his colleagues¹⁸⁸. These authors pointed out the necessity of a carefully taken history and the value of blood studies to differentiate allergic purpura from an acute abdominal condition. They added that the use of epinephrine may also be of value for establishing a definite diagnosis.

The determination of the causal factor of purpura before the institution of treatment is most important, and since this cannot always be accomplished, failure of therapy may result. Sternal puncture¹⁸⁹ to determine the presence or absence of megakaryocytes should be per-

179 Keil, H. Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, *Brit J Dermat* **49** 221, 1937

180 Kramer, P. H. Purpura Haemorrhagia After the Use of Sedormid, *Nederl tijdschr v geneesk* **8** 3345, 1937

181 van Andel, P., and Groen, J. Thrombopenic Purpura (Werlhof's Disease) After Use of Sedormid, *Nederl tijdschr v geneesk* **81** 3348, 1937

182 Schonberg, I. L. Purpuric and Scarlatiniform Eruption Following Sulfanilamide, *J A M A* **109** 1035 (Sept 25) 1937

183 Goodman, M. H., and Levy, C. S. The Development of a Cutaneous Eruption (Toxicodermatosis) During the Administration of Sulfanilamide, *J A M A* **109** 1009 (Sept 25) 1937

184 Padget, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **60** 887 (Nov) 1937

185 Wright, H. P., and Bacal, H. L. Allergic Tuberculous Purpura, *Am J Dis Child* **53** 1276 (May) 1937

186 Lytle, C. C., and Ward, D. F. Idiopathic Thrombopenic Purpura, *J Iowa M Soc* **27** 296, 1937

187 Squier, T. L., and Madison, F. W. Thrombocytopenic Purpura Due to Food Allergy, *J Allergy* **8** 143, 1937

188 Althausen, T. L., Deamer, W. C., and Kerr, W. J. False "Acute Abdomen," Henoch's Purpura and Abdominal Allergy, *Ann Surg* **106** 242, 1937

189 Goldhamer, S. M. Bone Marrow Studies in Purpura, unpublished data

formed before splenectomy is attempted. In many instances the removal of the spleen has been followed by little or no improvement. The failure of improvement may be due to the fact that the bone marrow is not producing platelets, hence splenectomy is an unnecessary procedure. Wintrobe¹⁷⁵ stated that splenectomy is not specific, Mettier and Purviance¹⁷⁰ stated the opinion that the removal of the spleen is of questionable value, Ainsworth¹⁶⁹ recommended this procedure.

Peck and his co-workers¹⁷¹ advised the use of snake venom. Eagle¹⁹⁰ studied the various types of venoms and their effectiveness and noted that about 50 per cent were of value. Roentgen therapy has been employed by Mettier and Purviance with good results, but Ainsworth concluded that its value is questionable. In cases of drug poisoning and allergy the inciting factor should be removed. Hildebrandt¹⁹¹ observed satisfactory results with vitamin C and iron, whereas Vervloet¹⁹² reported the opposite. Since spontaneous remissions are not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

HEMOPHILIA

The essential clinical features of hemophilia are its inheritance, the occurrence in males, a history of repeated hemorrhages, a prolonged clotting time and a normal bleeding time. The disease is transmitted according to the mendelian laws by the female. Bauer and Meller¹⁹³ said they were not entirely in accord with this view. They carefully reviewed the literature referable to the presence of hemophilia in women and stated that there is sufficient evidence to justify the assumption that hemophilia may exist in females. In support of this conclusion they cited 4 cases.

Included in the group of diseases associated with abnormal bleeding is a syndrome known as hereditary pseudohemophilia. Fowler¹⁹⁴ described 2 cases of this disease. The outstanding clinical features are hereditary transmission by either sex to either sex, occurrence at any

190 Eagle, H. Coagulation of Blood by Snake Venoms and Its Physiologic Significance, *J Exper Med* **65** 613, 1937.

191 Hildebrandt, A. Zur Behandlung starker Genitalblutungen bei essentieller Thrombopenie, *Med Welt* **11** 1103, 1937.

192 Vervloet, C. G. Treatment of Werlhof's Disease and Other Thrombopenic Forms of Purpura, *Nederl tijdschr v geneesk* **81** 3940, 1937.

193 Bauer, H., and Meller, J. Ueber weibliche Hamophilie, *Wien klin Wchnschr* **50** 495, 1937.

194 Fowler, W. M. Hereditary Pseudo-Hemophilia, *Am J M Sc* **193** 191, 1937.

age (usually late childhood or adolescence), recurrent hemorrhages from any organ (spontaneous or traumatic), normal platelet count, prolonged bleeding time and normal clotting time

Pachman¹⁹⁵ described 3 cases of hemophilia in Negroes, in 2 of which there was a definite family history. He stressed the fact that the occurrence of this disease in Negroes is rare. Placental extract was of value in 1 of 2 cases. Estrogenic substance (theelin) proved helpful in 1 instance.

The defect of the coagulation mechanism has recently received considerable attention. Bendien and van Creveld¹⁹⁶ isolated a substance from normal fresh serum or plasma which will promote coagulation in blood of a hemophiliac person. The investigators said they believed that this factor is absent from the blood in hemophilia. Patek and Taylor¹⁹⁷ and Pohle and Taylor¹⁹⁸ also have isolated a substance from normal plasma which promotes coagulation. A detailed method for obtaining this material is described by them. Various experiments employing the use of this product with favorable results are reported. The effect of trypsin on the clotting of blood in hemophiliac persons was studied by Tyson and West¹⁹⁹. The authors concluded that trypsin accelerates coagulation of the blood *in vitro* and that its action is similar to that of thrombin.

In spite of the important experiments which have been performed, the specific treatment of hemophilia still remains a mystery. Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen, cephalin, calcium, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts. Kohl²⁰⁰ reported satisfactory results with histidine administered enterally and parenterally. The value of estrogenic substance has yet to be established. Pohle and

195 Pachman, D. J. Hemophilia in Negroes, *J. Pediat.* **10** 809, 1937.

196 Bendien, W. M., and van Creveld, S. Investigations on Hemophilia, *Am. J. Dis. Child.* **54** 713 (Oct.) 1937.

197 Patek, A. J., and Taylor, F. H. L. Hemophilia. Some Properties of a Substance Obtained from Normal Human Plasma Effective in Accelerating the Coagulation of Hemophilic Blood, *J. Clin. Investigation* **16** 113, 1937.

198 Pohle, F. J., and Taylor, F. H. L. The Coagulation Defect in Hemophilia. The Effect in Hemophilia of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma, *J. Clin. Investigation* **16** 741, 1937.

199 Tyson, T. L., and West, R. Effect of Trypsin on the Clotting of the Blood in Hemophilia, *Proc. Soc. Exper. Biol. & Med.* **36** 494, 1937.

200 Kohl, H. Histidinbehandlung der Hamophilie, *Ztschr. f. klin. Med.* **132** 40, 1937.

Maddock²⁰¹ recommended the use of maggot therapy for infected wounds. They stated that the danger of hemorrhage is minimized and the infection is readily eliminated.

BLOOD CLOTTING

The most extensive review concerning the necessary factors for coagulation and the mechanism involved has been published by Eagle²⁰². Heilingbrunner and Schorcher²⁰³ have pointed out that cessation of bleeding and coagulation are independent processes. Bleeding from vessels is controlled by the contraction of the vessel walls and as long as hemorrhage continues a clot cannot form. The nature of the clot has received considerable attention from McKhann and his co-workers²⁰⁴. They described it as a firm gelatinous mass with meshes of fibrin, containing variable amounts of water and some formed elements of the blood. Variations in the clot content may occur in different blood dyscrasias.

Several interesting experiments relating to coagulation of the blood have been performed. Terazawa and his colleagues²⁰⁵ determined the effect of vitamin C on coagulation. They said that they believed that it accelerates the process by increasing the number of platelets and the amount of thrombin and fibrinogen. Taliaferro and Haag²⁰⁶ stated that congo red in small amounts decreases the coagulation time but that large doses tend to have the opposite effect. Delayed or prolonged coagulation subsequent to anaphylactic shock was said by Eagle and his co-workers²⁰⁷ to be due to an increased amount of antithrombin. Brinkhous, Smith and Warner²⁰⁸ stated that the hemorrhagic disease of

201 Pohle, F. J., and Maddock, S. Maggot Therapy in an Infected Wound in Hemophilia, *J. A. M. A.* **109** 2055 (Dec 18) 1937

202 Eagle, H. Recent Advances in the Blood Coagulation Problem, *Medicine* **16** 95, 1937

203 Heilingbrunner and Schorcher, F. Die Blutstillung mit körpereigenem Gewebe, *Deutsche Ztschr. f. Chir.* **248** 475, 1937

204 McKhann, C. F., Chu, F. T., Green, A. A., and Eley, R. C. Character of the Blood Clot in Normal Persons and in Hemophiliacs, *Tr. Am. Pediat. Soc.* **48** 61, 1936

205 Terazawa, N., Takeda, K., and Mizoguchi, K. Effect of Vitamin C on Coagulability of Rabbit Blood, *Jap. J. Obst. & Gynec.* **20** 550, 1937

206 Taliaferro, M. A., and Haag, H. B. Toxicity and Effect of Congo Red upon Blood Coagulation, *Am. J. M. Sc.* **193** 626, 1937

207 Eagle, H., Johnston, C. G., and Ravdin, I. S. On the Prolonged Coagulation Time Subsequent to Anaphylactic Shock, *Bull. Johns Hopkins Hosp.* **60** 428, 1937

208 Brinkhous, K. M., Smith, H. P., and Warner, E. D. Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of New Born, *Am. J. M. Sc.* **193** 475, 1937

newborn infants is probably due to decreased amounts of prothrombin, which condition may be readily corrected with transfusions. The effects of histidine on the clot mechanism were studied by Bloch, Kosse and Necheles,²⁰⁹ who concluded that it has no apparent effect. The role of calcium in clot formation was investigated by Ferguson²¹⁰. In his opinion, calcium is probably a thrombin stabilizer.

Dam and his co-workers²¹¹ first suggested that a certain dietary deficiency in animals produces a marked hemorrhagic tendency. The missing substance was termed vitamin K. It is fat soluble and is present in hog liver oil, cabbage, spinach, tomatoes and alfalfa. It occurs in a nonsterol fraction of unsaponifiable fat, and it closely resembles vitamin E in solubility and in resistance to heat.

Almquist²¹² isolated vitamin K and described a method for concentrating it. Almquist and Stokstad²¹³ further demonstrated that chicks with a hemorrhagic tendency can be cured with an extract from alfalfa. The vitamin was described by Almquist as a nonnitrogenous substance with an aromatic nucleus, it does not contain phosphorus, sulfur or a sterol ring. It is alkali labile, heat stable and optically inactive, with a molecular weight of about 600. Ultraviolet light, aluminum oxide and magnesium oxide destroy its activity.

Schonheyder²¹⁴ demonstrated that vitamin K is present in prothrombin of normal chicks but absent or inactive in chicks with hemorrhagic disease. Roderick²¹⁵ showed that a marked hemorrhagic tendency exists in animals fed spoiled sweet clover hay, and that this tendency to bleed is related to a deficiency of prothrombin. Dam,

209 Bloch, L., Kosse, J., and Necheles, H. Clotting Time of Blood Following Administration of Histidine, *J A M A* **109** 204 (July 17) 1937.

210 Ferguson, J. H. An Intermediary Calcium Complex in Blood Coagulation, *Am J Physiol* **119** 755, 1937.

211 Dam, H. Haemorrhages in Chicks Reared on Artificial Diets. New Deficiency Disease, *Nature, London* **133** 909, 1934, Antihaemorrhagic Vitamin of the Chick. Occurrence and Chemical Nature, *ibid* **135** 652, 1935, Antihaemorrhagic Vitamin of the Chick, *Biochem J* **29** 1273, 1935. Dam, H., Schonheyder, F., and Lewis, L. Requirement for Vitamin K of Some Different Species of Animals, *ibid* **31** 22, 1937. Dam, H., Schonheyder, F., and Tage-Hansen, E. Studies on the Mode of Action of Vitamin K, *ibid* **30** 1075, 1936.

212 Almquist, H. J. Anti-Hemorrhagic Vitamin, *Poultry Sc* **16** 166, 1937, Further Studies on the Anti-Hemorrhagic Vitamin, *J Biol Chem* **120** 635, 1937.

213 Almquist, H. J., and Stokstad, E. L. R. Hemorrhagic Chick Disease of Dietary Origin, *J Biol Chem* **111** 105, 1935.

214 Schonheyder, F. Anti-Hemorrhagic Vitamin of the Chick. Measurement and Biological Action, *Nature, London* **135** 653, 1935, Quantitative Determination of Vitamin K, *Biochem J* **30** 890, 1936.

215 Roderick, L. M. Pathology of Sweet Clover Disease in Cattle, *J Am Vet M A* **74** 314, 1929, A Problem in the Coagulation of the Blood. Sweet Clover Disease of Cattle, *Am J Physiol* **96** 413, 1931.

Schonheyder and Lewis determined the requirements of vitamin K for various species of animals. In some species hemorrhagic symptoms developed rapidly with a deficient diet and responded readily to substitute treatment, in others, symptoms developed slowly and in some the deficient diet had no effect. The authors explained these differences by stating that (1) some animals may not need vitamin K, (2) others may synthesize it and (3) bacteria may produce vitamin K in the intestines of certain animals. They have never observed the disease in man and reported that vitamin K is of no value to hemophilic persons.

The so-called vitamin T factor (fat soluble) was studied by Schiff and Hirschberger²¹⁶. The vitamin is present in sesame oil and is not present in cod liver oil and olive oil. When administered in therapeutic amounts to children, it produced a marked increase in the number of platelets.

BANTI'S DISEASE

An accurate appreciation of Banti's disease, as described by Banti in 1881 and 1894, may be obtained from translations²¹⁷ of his original articles. Banti stated that the course of the disease could be divided into three stages which lasted for several years. He postulated that the etiologic agent was an unidentified toxic substance that was carried to the spleen, with secondary involvement of the liver. The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver. The treatment was splenectomy.

The existence of this disease at present is questioned²¹⁸. The pathologic changes, which were thought by Banti to be specific, have been shown by Thompson and his co-workers²¹⁹ to be due to increased pressure in the splenic vein, with secondary effects in the spleen. Gravano²²⁰ also said he believed that primary splenomegaly involves the portal and splenic veins or the splenic veins alone. The former is

216 Schiff, E, and Hirschberger, C. Ueber den T-Factor, *Jahrb f Kinderh* **150** 247, 1937, Thrombocytosis Produced by a Hitherto Unknown Substance—"Fat-Soluble T Factor," *Am J Dis Child* **53** 32 (Jan, pt 1) 1937.

217 Banti, G. Splenomegaly with Cirrhosis of the Liver, translation, *M Classics* **1** 907, 1937, Splenomegaly with Cirrhosis of the Liver, translation, *ibid* **1** 913, 1937.

218 Lawrence, J. S. Indications for Splenectomy in a Medical Practice, *Internat Clin* **2** 221, 1937.

219 Thompson, W. P., Caughey, J. L., Whipple, A. O., and Rousselot, L. M. Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), *J Clin Investigation* **16** 571, 1937.

220 Gravano, L. Esplenomegalia primitiva congestiva, *Semana med* **1** 488, 1937.

termed the diffuse intraperiphlebitic type and is toxic or infectious in nature, the latter is the cryptogenic form, and the etiologic factor is unknown

The most commonly observed symptoms and signs, as well as the outstanding differential diagnostic features, have been reviewed by Foti²²¹ Splenomegaly, weakness, hemorrhage, enlargement of the liver, jaundice and ascites are the most common findings Fittipaldi²²² described the case of a young girl with miliary tuberculosis who presented the clinical picture of Banti's disease He said he believed that cirrhosis of the liver may be due to chronic intoxication from tuberculous toxins from the spleen which enter the hepatic viscera through the portal system The hematemesis which is so common was said by Serafin²²³ to be the result of mechanical and pathologic changes in the spleen He concluded that the enlargement of the spleen compresses the lienal vein and causes secondary traumatic changes in the blood vessels, with the production of aseptic thrombophlebitis The physiopathologic factor is an increase in the pressure in the venous system, as previously mentioned

For several years the accepted treatment for Banti's disease has been splenectomy Serafin²²³ recommended removal of the spleen early in the course of the disease He also said that anastomosis of the portal system and the inferior vena cava may be of some value Gravano²²⁰ advised splenectomy for the cryptogenic form of splenomegaly but not for the diffuse intraperiphlebitic type Serbin,²²⁴ in discussing the presence of splenomegaly in pregnancy, stated that transfusions and splenectomy are indicated to prevent the progress of the disease Bergeret and Caroli²²⁵ stated that splenectomy is beneficial in selected cases only An unusual case of splenic anemia which was benefited by splenectomy was reported by Manson-Bahr, Strauss and Ruttan²²⁶ In opposition to these observations, Lawrence said he doubted the existence of the disease and stated that splenectomy is of no value

221 Foti, A Clinical Consideration of Splenic Enlargement, *M Rec* **145** 60, 1937

222 Fittipaldi, C Splenomegalia tubercolare con cirrosi epatica e sindromi bantiene tubercolari (contributo anatomo-patologico), *Pathologica* **29** 275, 1937

223 Serafin, P J Banti's Disease with Gastrorrhagias and Thrombophlebitis, *Am J Surg* **35** 76, 1937

224 Serbin, W B Splenomegaly in Pregnancy, *Am J Obst & Gynec* **34** 486, 1937

225 Bergeret, A, and Caroli, J Suites éloignées de la splénectomie au cours des cirrhoses du foie, *Bull et mém Soc méd d hôp de Paris* **53** 1019, 1937

226 Manson-Bahr, P H, Strauss, J N, and Ruttan, H R An Unusual Case of Splenic Anaemia Treated by Splenectomy, *Lancet* **2** 1518, 1936

ERYTHROBLASTOSIS FOETALIS

In erythroblastosis foetalis Javert ²²⁷ noted that the placenta may be yellow, the vernix deep yellow, and the fluid which appears on rupture of the membranes, amber. The newborn child shows a palpable liver and spleen. In the birth of these infants it is preferable to use no anesthetic. Erythroblasts appear in the blood of the infant and in the fetal capillaries of the placenta in increased numbers. At the Woman's Clinic of New York the incidence noted in 1936 was 1/400 infants, but the actual incidence is probably greater.

Nittis and Spiliopulos ²²⁸ noted a similarity between erythroblastic anemia and congenital malaria both as to blood and as to skeletal changes. Seven of 8 patients with erythroblastic anemia were apparently completely relieved of all their clinical and hematologic symptoms after a maximum period of three months of quinine therapy.

Caffey ⁶⁸ made a roentgen study of 21 cases of erythroblastic anemia. The earliest lesion of the skull was a thickening of the lower frontal squamosa. Radial striations developed first in the anterior portion of the parietal bones near the sagittal suture, and the frontal bone was the site of the earliest and most marked thickening. The first change in the long bones was dilatation of the medullary canals, with atrophy of the cortical and cancellous bone. Reticulation of the long bones did not appear until several months later. In 15 cases of sickle cell anemia, no significant changes were observed in the long bones, but in 10 cases there was thickening of the calvarium similar to that seen in cases of erythroblastic anemia. Vertical striations of the skull were not present, but in contrast to erythroblastic anemia, the parietal bones showed more marked involvement than the frontal bones. In 6 cases of chronic hemolytic icterus there were no significant changes in the long bones. Two of the patients showed thickening and striation of the calvarium similar to those of erythroblastic anemia, but the parietal bones were more involved than the frontal.

In this connection the observations of Wakefield, Dellinger and Camp ²²⁹ on the osseous remains of the mound builders in eastern Arkansas are of interest. Two skulls and the femurs and tibias showed characteristic changes suggesting sickle cell anemia, congenital hemolytic jaundice and erythroblastic anemia, similar to that usually found in members of the Mediterranean races.

²²⁷ Javert, C. T. Erythroblastosis Fetalis as a Cause of Infantile Mortality. Preliminary Report, *Am J Obst & Gynec* **34** 1042, 1937.

²²⁸ Nittis, S., and Spiliopulos, G. Similarity of Erythroblastic Anemia and Chronic or Congenital Malaria. Successful Treatment of Eight Patients with Quinine, *Am J Dis Child* **54** 60 (July) 1937.

²²⁹ Wakefield, E. G., Dellinger, S. C., and Camp, J. D. A Study of the Osseous Remains of the "Mound Builders" of Eastern Arkansas, *Am J M Sc* **193** 488, 1937.

SICKLE CELL ANEMIA

Robinson²³⁰ found that red blood corpuscles aspirated from the sternum of a patient with sickle cell anemia showed the same tendency to sickle as blood from other regions

Cardozo²³¹ found that both the blood grouping and the distribution of immune agglutinogens M and N did not differ materially in patients showing sickling from those of normal persons. In Chicago the incidence of sickling was 9.42 per cent in Negroes and 0.32 per cent in non-Negroes. The average incidence given in other available reports was 7.44 per cent. No specific agglutinogens could be demonstrated. Serum was not necessary for the sickling of the erythrocytes, and the tendency remained in the cell, no matter how long it was preserved, provided the cell itself remained intact.

Diggs, Pulliam and King²³² studied 39 cases of sickle cell anemia roentgenologically and were able to study the bones at necropsy in 8 cases. The primary involvement was in the marrow. The factor of hyperplasia of the marrow as well as osteoporosis was present. Sclerosis was most marked in the long bones (see also the reference to Caffey in the section on erythroblastic anemia).

The cardiac complications were emphasized in the case reported by King and Janeway²³³. Johnson and Townsend²³⁴ summarized their experiences in 30 cases, and Dale²³⁵ reported additional data.

Lewis'²³⁶ patient was pregnant and had a history of three abortions at four to seven months. The author suggested sickle cell anemia as an etiologic agent in habitual abortion. However, the patient reported on by Sodeman and Burch²³⁷ had an uneventful delivery of an infant which subsequently showed sickle cell anemia.

230 Robinson, H. A. Sickle Cell Anemia, Bone Marrow Studies, J. Michigan M. Soc. **36** 964, 1937.

231 Cardozo, W. W. Immunologic Studies of Sickle Cell Anemia, Arch. Int. Med. **60** 623 (Oct.) 1937.

232 Diggs, L. W., Pulliam, H. N., and King, J. C. Bone Changes in Sickle Cell Anemia, South. M. J. **30** 249, 1937.

233 King, J. T., Jr., and Janeway, C. A. Sickle Cell Anemia with Cardiac Complications, Internat. Clin. **3** 41, 1937.

234 Johnson, F. B., and Townsend, E. W. Sickle Cell Anemia. Report of Thirty Cases, South. Med. & Surg. **99** 377, 1937.

235 Dale, G. C. Sickle Cell Anemia, South. Med. & Surg. **99** 14, 1937.

236 Lewis, A. W., Jr. Sickle Cell Anemia with Pregnancy, Am. J. Obst. & Gynec. **33** 667, 1937.

237 Sodeman, W. A., and Burch, G. E. Pregnancy in Active Sickle Cell Anemia, New Orleans M. & S. J. **90** 156, 1937.

Harden²³⁸ pointed out the "hair-on-end" appearance in roentgenograms of the skulls of patients with long-standing sickle cell anemia. There was marked tortuosity of the retinal blood vessels in his patient, a 9 year old Negro. The superficial temporal vessels were also extremely tortuous and thickened.

Haden and Evans²³⁹ reported the occurrence of sickle cell anemia in 2 patients of Sicilian ancestry, in whom no known Negro admixture existed. There was definite symptomatic improvement after splenectomy, although mild hemolytic anemia persisted. The authors said they considered that splenectomy has some value in this disease.

Hansen-Pruss²⁴⁰ found that by supravital staining with brilliant cresyl blue or janus green the maximum sickling phenomenon of susceptible red blood cells could be elicited in from four to five hours instead of twenty or more hours by the method of unstained moist preparation. With this technic, 14 per cent of an unselected group of 100 Negroes showed the trait, as contrasted with the reported average of 6 per cent with the older methods.

INFECTIOUS MONONUCLEOSIS

The etiology of infectious mononucleosis is unknown. Various organisms have been isolated and described as the causative factor, but none of the work has been confirmed. Nyfeldt²⁴¹ recently studied the etiology of this disease and found that the group of *Listerellae* were pathogenic for both men and animals.

The clinical features of the disease and the various procedures necessary for the establishment of the diagnosis have been summarized by Durupt²⁴². Recognition of the condition is most important because of its resemblance to the hemocytoblastomas, which have a fatal prognosis. Israels²⁴³ pointed out the similarity of infectious mononucleosis and monocytic leukemia but stated that the differences in the blood picture and the sheep cell agglutination reaction should aid in the differential

238 Harden, A. S., Jr. Sickle Cell Anemia. Changes in Vessels and in Bones, *Am J Dis Child* **54** 1045 (Nov) 1937.

239 Haden, R. L., and Evans, F. D. Sickle Cell Anemia in the White Race. Improvement in Two Cases Following Splenectomy, *Arch Int Med* **60** 133 (July) 1937.

240 Hansen-Pruss, O. C. Experimental Studies of Sickling of Red Blood Cells, *J Lab & Clin Med* **22** 311, 1936.

241 Nyfeldt, A. Studies on the Etiology of Infectious Mononucleosis, *Hygiea* **99** 433, 1937.

242 Durupt, A. Le diagnostic serologique des mononucléoses infectieuses, *Presse med* **45** 1219, 1937.

243 Israels, M. C. G. Infectious Mononucleosis (Glandular Fever) and Monocytic Leukemia, *Brit M J* **1** 601, 1937.

diagnosis Ustvedt²⁴⁴ stressed the difficulties encountered in differentiating infectious mononucleosis from acute myeloblastic leukemia He suggested the use of sternal puncture as a means of establishing the diagnosis

Since Paul and Bunnell devised an agglutination test which appears to be practically specific for infectious mononucleosis, many investigators have substantiated their work A careful serologic study of 30 cases of infectious mononucleosis was made by Davidsohn²⁴⁵ His study was based on a modified technic which he devised In his opinion the differential test is most important for (1) confirmation of the diagnosis of infectious mononucleosis in cases in which there is a definite clinical and hematologic picture, (2) exclusion of cases in which the condition simulates infectious mononucleosis, with similar blood findings, (3) establishment of the diagnosis in cases in which the blood pictures is atypical, and (4) aid in the recognition of cases of late infectious mononucleosis and cases in which the condition is complicated by injections of serum

AGRANULOCYTOSIS

Since the original description of agranulocytic angina by Schultz, in 1922, the disease has been firmly established as a clinical entity Multiple etiologic factors have been recognized, but the mechanism involved in the production of the syndrome is still obscure Schattenberg²⁴⁶ stated that the leukopoietic disorder may result from endocrine disturbances, radiation, infection, allergy or the toxic effect of drugs To this list may be added protein shock

The drug most commonly indicted as a cause of agranulocytosis is aminopyrine Davis and Frissell²⁴⁷ gave aminopyrine daily to 32 patients for varying periods up to three months without demonstrating any alteration in the white blood cell count They also observed patients who had used the drug for more than four years without dangerous clinical symptoms Of 50 patients who received cutaneous tests with aminopyrine, only 1, who was sensitive to the drug, reacted positively Davis and Frissell also reported 20 cases of agranulocytosis, 9 in patients who were known to have taken aminopyrine and 1 after the ingestion of antipyrine methylaminomethane sodium sulfonate

244 Ustvedt, H J Infectious Mononucleosis, *Norsk mag f lægevidensk* **98** 139, 1937

245 Davidsohn, I Serologic Diagnosis of Infectious Mononucleosis, *J A M A* **108** 289 (Jan 23) 1937

246 Schattenberg, H J Present Day Conception of Agranulocytic Angina, *New Orleans M & S J* **90** 78, 1937

247 Davis, J S, and Frissell, L F Amidopyrine Hypersensitivity, *J Lab & Clin Med* **23** 107, 1937

Magee²⁴⁸ cited 3 cases of agranulocytosis. The use of aminopyrine was definitely established in 2. Shapiro and his associates²⁴⁹ observed a man in whom agranulocytosis developed after he had taken cinchophen, 0.5 Gm three times daily for about three weeks. They pointed out that cinchophen (phenylquinoline carboxylic acid) under certain conditions may yield benzene or nitrophenol, either of which can cause a paralyzing effect on the bone marrow. A fatal case of agranulocytosis due to intramuscular injections of a bismuth preparation was reported by Dowds,²⁵⁰ who specifically stated that aminopyrine was not a contributing factor. Embleton²⁵¹ reported a case of rhythmic neutropenia in a middle-aged woman. The cause was not determined. Agranulocytosis associated with purpura and tuberculous laryngitis was noted by Taylor²⁵². The neutropenia followed the administration of a gold compound. Das Gupta and Witts²⁵³ observed a case of agranulocytosis with a characteristic bone marrow picture after the administration of gold. The possibility of aminopyrine intoxication was considered, but no changes in the peripheral blood were observed with test doses. Agranulocytosis due to sulfanilamide poisoning was reported by Young²⁵⁴ and by Jennings and Southwell-Sander²⁵⁵.

Several theories have been advanced in an attempt to explain the mechanism of agranulocytosis. Fitz-Hugh²⁵⁶ stated that the theory of "maturation arrest" cannot account for the sudden disappearance of granulocytes from the peripheral blood. A more likely explanation, he concluded, of the "shock mechanism" of this phenomenon is the adhesion of the leukocytes to the capillary endothelium. Holten²⁵⁷ offered the hypothesis that the bone marrow reaction is an Arthus phenomenon.

248 Magee, C. G. Agranulocytosis, *Practitioner* **139** 185, 1937.

249 Shapiro, S., and Lehman, L. A Case of Agranulocytosis Following Ingestion of Cinchophen, *Am J M Sc* **192** 705, 1936.

250 Dowds, J. H. Agranulocytic Angina Following Bismuth Injections in a Case of Syphilis, *Brit M J* **2** 620, 1937.

251 Embleton, D. Rhythmical Neutropenia with Recurrent Buccal Ulceration, *Proc Roy Soc Med* **30** 980, 1937.

252 Taylor, A. B. Agranulocytic Angina, Purpura and Tuberculous Laryngitis Complicating Pulmonary Tuberculosis, with Recovery, *Lancet* **2** 73, 1937.

253 Das Gupta, C. R., and Witts, L. J. Chronic Agranulocytosis Successfully Treated with Liver, *Brit M J* **1** 1197, 1937.

254 Young, C. J. Agranulocytosis and Para-Amino-Benzene Sulphonamide, *Brit M J* **2** 105, 1937.

255 Jennings, G. H., and Southwell-Sander, G. Anemia and Agranulocytosis During Sulfanilamide Therapy, *Lancet* **2** 898, 1937.

256 Fitz-Hugh, T., Jr. Etiology and Pathology of Agranulocytic Angina. Present Day Findings and Hypotheses, *Am J Clin Path* **7** 524, 1937.

257 Holten, C. Considerations and Experiments on Hypersensitive Nature of Amidopyrine Agranulocytosis, *Am J M Sc* **194** 229, 1937.

localized to the leukopoietic part of the marrow. He failed to demonstrate passive transfer of aminopyrine sensitivity, nor was he able to show cutaneous sensitivity in a patient who was hypersensitive to the drug when administered orally. Golden and Silverglade²⁵⁸ attempted to produce agranulocytosis in guinea pigs by sensitizing them with a benzene compound but were unable to demonstrate any changes in the leukocyte count.

Davis and Frissell²⁴⁷ summarized the literature regarding aminopyrine hypersensitivity and found discussions of three theories to explain the role of aminopyrine intoxication in the production of granulocytopenia. 1. All drugs with the benzene nucleus, or the benzene nucleus in association with an amino group, are per se toxic, presumably to the bone marrow. 2. Aminopyrine is semispecific for the bone marrow and produces a direct intoxication of the leukopoietic tissue. 3. The hemopoietic changes are the result of an allergic reaction. In addition to the various theories suggested, none of which is adequate in all instances, it should be emphasized that fatigue, infection, age and menstruation play an important part in the production of the disease.

The pathologic changes occurring in agranulocytosis are distinct. The bone marrow shows a maturation arrest at the myeloblast-myelocyte stage,²⁵⁹ few, if any, of the myeloid cells migrate into the peripheral blood. Ulcerations of the mucous membranes are characterized by tissue necrosis without a neutrophil inflammatory reaction and are subject to secondary invasion by bacteria. Recovery is initiated by leukopoietic hyperplasia of the marrow, a myelocyte crisis in the peripheral blood, monocytosis, the normal production of polymorphonuclear leukocytes and elimination of the infection in the tissues.

In the treatment of agranulocytosis, drugs which may play a part in the etiology of the disease should, of course, be withdrawn. Repeated small transfusions are frequently indicated. Intramuscular injections of pentnucleotide solution or of liver extract are often valuable. Maiberg and Wiles²⁶⁰ stressed the efficacy of yellow bone marrow.

BLOOD CHANGES FROM SULFANILAMIDE AND RELATED COMPOUNDS

With the increasing use of sulfanilamide and related compounds in certain bacterial infections, many reports on changes in the blood have appeared. Harvey and Janeway^{70b} described 3 cases of a rapidly devel-

258 Golden, A., and Silverglade, A. Sensitization of Guinea Pigs to Cyclic Compounds and Effect on the Hematopoietic System, *Proc Soc Exper Biol & Med* **37** 400, 1937.

259 Beckman, H. Pharmacological Analysis of Agranulocytosis, *Tr Am Therap Soc* **36** 41, 1936. Schattenberg²⁴⁶ Fitz-Hugh²⁵⁶

260 Marberg, C. M., and Wiles, H. O. Yellow Bone Marrow Extracts in Granulocytopenia. Preliminary Report, *J A M A* **109** 1965 (Dec 11) 1937.

oping hemolytic anemia characterized by leukocytosis and immature red and white blood cells in the peripheral circulation. Recovery followed cessation of the administration of the drug and the giving of blood transfusions. A striking resemblance to the hemolytic crisis produced by the use of phenylhydrazine was noted. The reaction is an individual response to the drug. Later 8 more cases of this type were noted (Bohlman²⁶¹), hemoglobinuria being noted in 1 case.

Long and Bliss²⁶² noted 7 cases in which hemolytic anemia developed, characterized by a sudden fall in the hemoglobin value and red blood cell count and the appearance of macrocytosis, anisocytosis, poikilocytosis, leukocytosis, normoblastosis and reticulocytosis. Of the 7 patients, 6 were jaundiced, and all showed urobilinuria. All the patients recovered, 5 of them after one or more blood transfusions. In another patient neutropenia developed, but test doses did not elicit a similar response after recovery, showing a difference from aminopyrine sensitivity in this respect. One of Carey's²⁶³ 38 patients showed a fall in the red blood cell count from 5,000,000 to 2,000,000 per cubic millimeter during ten days (52 Gm of sulfanilamide). In McQuarrie's²⁶⁴ case hemolytic anemia developed after four days of therapy, and transfusions were ineffective in saving the patient's life. In these cases there appeared to be no close correlation between the dosage of the drug and the development of anemia. Kohn's^{70a} patient, a 1 year old child, showed hemoglobinuria, leukocytosis and immature red and white blood cells. Recovery was rapid. Common features in sulfanilamide anemia were fever and evidence of intense illness.

Numerous reports of extreme neutropenia following sulfanilamide therapy, frequently fatal, have appeared (Bernstein,²⁶⁵ Borst,²⁶⁶ Jennings and Southwell-Sander,²⁶⁵ Massell,²⁶⁷ McIntosh, Wilcox and

261 Bohlman, H. R. The Use of Sulphanilamide, *Dis. of Chest* **3** 24, 1937.

262 Long, P. H., and Bliss, E. A. The Clinical Use of Sulphanilamide and Its Derivatives in the Treatment of Infectious Diseases, *Ann. Int. Med.* **11** 575, 1937.

263 Carey, B. W., Jr. The Use of Para-Aminobenzenesulphonamide and Its Derivatives in the Treatment of Infections Due to the Beta Streptococcus Hemolyticus, the Meningococcus and the Gonococcus. Report of Thirty-Eight Cases, *J. Pediat.* **11** 202, 1937.

264 McQuarrie, I. Report on Cases Treated with Sulphanilamide (Prontosil and Prontylin), *J. Pediat.* **11** 188, 1937.

265 Bernstein, S. S. Report on the Use of Sulphanilamide at the Children's Hospital of Michigan, *J. Pediat.* **11** 198, 1937.

266 Borst, J. G. G. Death from Agranulocytosis After Treatment with Prontosil Flavum, *Lancet* **1** 1519, 1937.

267 Massell, B. F. Studies on the Use of Prontylin in Rheumatic Fever, *New England J. Med.* **216** 487, 1937.

Wright,²⁶⁸ McQuarrie,²⁶⁴ Mitchell and Trachsler,²⁶⁹ Model,²⁷⁰ Plumer,²⁷¹ Trumper,²⁷² and Young²⁵⁴)

In some patients cyanosis has developed, with methemoglobinemia and sulfhemoglobinemia (Archer and Discombe,²⁷³ Bensley and Ross,²⁷⁴ Daniels,²⁷⁵ Discombe,²⁷⁶ Frost,²⁷⁷ Kane,²⁷⁸ Paton and Eaton²⁷⁹ and Stoness²⁸⁰ These substances have been demonstrated in the blood of patients Marshall and Walzl²⁸¹ suggested that the dark color may be due to a product of the drug itself

HODGKIN'S DISEASE AND LYMPHOSARCOMA

Medlar, Hornbaker and Ordway²⁸² presented additional data supporting the theory of Hodgkin's disease as a neoplasm of megakaryocytes In the blood of patients with Hodgkin's disease many monocytes are atypical, and it is possible that these are really young megakaryocytes

268 McIntosh, R, Wilcox, D A, and Wright, F H Results of Sulphanilamide Treatment at the Babies' Hospital, New York City, *J Pediat* **11** 167, 1937

269 Mitchell, A G, and Trachsler, W H Report on the Use of Sulphanilamide and Its Derivatives at the Children's Hospital, Cincinnati, *J Pediat* **11** 183, 1937

270 Model, A Agranulocytosis and Para-Aminobenzenesulphonamide, *Brit M J* **2** 295, 1937

271 Plumer, H E Neutropenia Occurring During the Use of Prontylin, *New England J Med* **216** 711, 1937

272 Trumper, A Prontylin and Prontosil, *New England J Med* **216** 857, 1937

273 Archer, H E, and Discombe, G Sulphaemoglobinaemia Its Cause and Prevention, *Lancet* **2** 432, 1937

274 Bensley, E H, and Ross, J B Methaemoglobinemia Due to Sulphanilamide, *Canada M A J* **37** 62, 1937

275 Daniels, A P Case of Sulphaemoglobinaemia Due to the Simultaneous Use of Magnesium Sulphate and Sulphanilamide, *Nederl tijdschr v geneesk* **81** 1837, 1937

276 Discombe, G Sulphaemoglobinaemia Following Sulphanilamide Treatment, *Lancet* **1** 626, 1937

277 Frost, L D B Sulphaemoglobinaemia Following Antistreptococcal Chemotherapy, *Lancet* **1** 5110, 1937

278 Kane, F F Case of Sulphaemoglobinaemia Following Administration of Drugs of Sulphonamide Group, *Ulster M J* **6** 144, 1937

279 Paton, J P J, and Eaton, J C Sulphaemoglobinaemia and Methaemoglobinaemia Following the Administration of P-Aminobenzenesulphonamide, *Lancet* **1** 1159, 1937

280 Stoness, J F Methemoglobinemia and Prontylin, *New York State J Med* **37** 1139, 1937

281 Marshall, E K, and Walzl, E On the Cyanosis from Sulphanilamide, *Bull Johns Hopkins Hosp* **61** 140, 1937

282 Medlar, E M, Hornbaker, J H, and Ordway, W H Interpretation of the Nature of Hodgkin's Disease Further Studies, *Folia haemat* **57** 52, 1937

Jackson²⁸³ proposed a classification for Hodgkin's disease and allied disorders. The classification, on a cytologic basis, is as follows: (1) lymphocytoma, lymphosarcoma, lymphatic leukemia, diffuse intra-glandular hypertrophy of lymphoid tissue, (2) reticulum cell sarcoma, early Hodgkin's disease, Hodgkin's disease and Hodgkin's sarcoma. The members of this group are considered as varying manifestations of the same neoplastic tendency. The maximum duration of Hodgkin's sarcoma is rarely more than three years, that of Hodgkin's disease, ten years, that of lymphosarcoma, rarely three years and never ten years, that of reticulum cell sarcoma, rarely ten years, but with appropriate treatment, ten to fifteen years.

In the report of the Metropolitan Life Insurance Company⁵¹ for the years 1921 to 1935, it is stated that 1,877 persons died of Hodgkin's disease, an incidence of 0.9 per cent. There were 950 white males, 104 Negroes, 732 white females and 91 Negresses. The death rate per hundred thousand was 0.8.

Bacaloglu and Enachescu²⁸⁴ studied the problem of abdominal Hodgkin's disease. Undulating fever lasting about a week, with gastrointestinal symptoms, diarrhea alternating with constipation, anemia, splenomegaly, leukopenia with relative neutrophilia, eosinopenia and variable monocytosis characterize the disease.

Roentgen therapy is advocated. Leukopenia marked Boyer's²⁸⁵ case, the leukocyte count fluctuating between 900 and 4,200 per cubic millimeter. A Pel-Ebstein type of fever was present. Peripheral lymphadenopathy was negligible. Typical abdominal Hodgkin's disease was evident at autopsy. Cutaneous ulcers, resulting from breakdown of nodules of the skin over Hodgkin's growths, were studied by Senear and Caro²⁸⁶. The ulcers may be mistaken for those of syphilis, sarcoma, mycosis, fungoides, epithelioma and tuberculosis. Pain is variable and occasionally is severe. Usually the lesions are punched out, with elevated margins. The ulcers are deep, and the underlying tissue may be involved extensively, the necrotic tissue may give rise to a fetid odor.

Jackson²⁸⁷ concluded that roentgen therapy does not, on the average, prolong life in Hodgkin's disease, but persistent treatment, especially

283 Jackson, H, Jr. Classification and Prognosis of Hodgkin's Disease and Allied Disorders, Surg, Gynec & Obst **64** 465, 1937

284 Bacaloglu, C, and Enachescu, M. La lymphogranulomatose abdominale maligne, Presse med **45** 76, 1937

285 Boyer, S, Jr. Hodgkin's Disease with Leukopenia, J A M A **108** 876 (March 13) 1937

286 Senear, F E, and Caro, M R. Ulcerative Hodgkin's Disease of Skin, Arch Dermat & Syph **35** 114 (Jan) 1937

287 Jackson, H, Jr. Notes on the Treatment and Prognosis of Hodgkin's Disease and Allied Disorders, M Clin North America **21** 361, 1937

when combined with blood transfusions and the use of viosterol in large amounts, can produce lasting benefits even in extreme cases. When Hodgkin's disease or reticulum cell sarcoma is localized in an early stage, radical measures offer hope for a permanent cure.

Frimann-Dahl²⁸⁸ gave an average of three years as the life expectancy for a patient with malignant lymphogranulomatosis. He found that roentgen treatment prolongs the life of the patient, the effects being more marked the earlier in the disease the treatment is given. With recurrence, irradiation becomes less effective.

Baensch²⁸⁹ advised small initial doses (150 roentgens) in the treatment of lymphogranuloma. After this, heliotherapy is advised. During the second stage of treatment, 300 roentgens is given over each field. The fever and glandular enlargements decrease four to six days after irradiation. Radium treatment is effective only when the lesions are superficial.

In the 20 year old patient of Loeper, Lemaire and Varay,²⁹⁰ tuberculosis flared up when the lymphogranuloma was irradiated.

Ducuing, Marques and Miletzky²⁹¹ found that "total roentgen therapy" was not without danger (effect on the blood). In Porta's²⁹² case severe herpes developed after roentgen therapy.

Hodgkin's disease at some time in its course may be fairly localized, numerous case reports present this aspect. Gordon²⁹³ described a case in which the ocular symptoms were marked. In Lebowich's²⁹⁴ case the bladder was involved. Cavazzani²⁹⁵ noted gross invasion of the pharynx, nasal fossae and paranasal sinuses. Cutaneous lesions were

288 Frimann-Dahl, J. Roentgen Treatment of Malignant Granulomatosis, *Norsk mag f lægevidensk* **97** 1273, 1936.

289 Baensch, W. Zur Strahlenbehandlung der Lymphogranulomatose, *Med Welt* **11** 464, 1937.

290 Loeper, M., Lemaire, A., and Varay, A. *Maladie de Hodgkin vraisemblable à localisation médiastino-pulmonaire et osseuse, tuberculose terminale*, *Bull et mém Soc méd d hôp de Paris* **53** 374, 1937.

291 Ducuing, J., Marques, P., and Miletzky, O. *Radiothérapie totale dans les maladies des organes hématopoïétiques, modifications sanguines et deductions pratiques*, *J de radiol et d'électrol* **21** 250, 1937.

292 Porta, R. *Erpete-zoster nella linfogranulomatosi sotto-posta a radio-terapia*, *Quaderni radiol* **1** 237, 1937.

293 Gordon, H. *Benign Lymphogranulomatosis with Ocular Symptoms*, *Proc Roy Soc Med* **30** 1057, 1937.

294 Lebowich, J. *Hodgkin's Disease Involving Bladder. Report of Case*, *Am J Cancer* **30** 758, 1937.

295 Cavazzani, F. *Linfogranuloma della faringe, delle fosse nasali e dei seni paranasali*, *Valsalva* **13** 205, 1937.

noted in the cases reported by Cottini,²⁹⁶ Nanta and Gadrat,²⁹⁷ Cerutti²⁹⁸ and Resl²⁹⁹. In Cabot case 23331³⁰⁰ there was generalized involvement.

Abdominal Hodgkin's disease often presents difficulties in diagnosis. Cases were described by Caselli,³⁰¹ Carnot and Lafitte,³⁰² Goldfarb³⁰³ (gastro-intestinal tract), Atakam³⁰⁴ (ileocecal region), Iacobovici and Stoia³⁰⁵ (stomach) and Lincke³⁰⁶ (small intestine). Redish³⁰⁷ noted Hodgkin's disease of the stomach, peripancreatic lymph nodes, spleen and anterior wall of the chest in a man aged 54 years. The symptoms consisted of a progressively enlarging mass on the anterior thoracic wall and gaseous eructations for eight months. The blood was not abnormal. Death followed an acute massive gastric hemorrhage. Redish's case is the twenty-third of this type recorded in which the diagnosis was confirmed at autopsy.

The various localizations, with consequent protean symptoms of Hodgkin's disease, have been well illustrated by Middleton³⁰⁸. Among his patients, from 6 to 84 years of age, outstanding symptoms in individual cases were pruritis, ulceration of a lesion with a draining sinus, involvement of the breast, neuritis, herpes zoster, osseous involvement, splenomegaly, hepatopathy, retroperitoneal lymphadenopathy, medias-

296 Cottini, G. B. Sul quadro cutaneo e glandulare in un caso di linfogranuloma maligno varieta inguinale, *Arch ital di dermat*, sif **13** 644, 1937.

297 Nanta, A., and Gadrat, J. Sur un granulome eosinophilique cutane, *Bull Soc franç de dermat et syph (Réunion dermat, Strasbourg)* **44** 1470, 1937.

298 Cerutti, P. Les manifestations cutanees dans la granulomatose maligne de Paltauf-Sternberg, *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1454, 1937.

299 Resl, V. Difficult Diagnosis in a Case of Lymphogranulomatosis Cutis, *Česka dermat* **17** 128, 1937.

300 Generalized Lymphoblastoma, Hodgkin's Type, Cabot Case 23331, *New England J Med* **217** 322, 1937.

301 Caselli, E. G. Linfogranulomatosis a localizacion abdominal en la infancia, *Rev Asoc med argent* **50** 302, 1937.

302 Carnot, P., and Lafitte, A. La forme hepato-splenique de la maladie de Hodgkin, *Paris med* **1** 447, 1937.

303 Goldfarb, S. J. Hodgkin's Disease of Gastro-Intestinal Tract, *J Mt Sinai Hosp* **4** 298, 1937.

304 Atakam, A. M. Lymphogranulomatosis of the Ileocecal Region, *Anadolu klin* **5** 25, 1937.

305 Iacobovici, I., and Stoia, I. Considerations sur un cas de lymphogranulomatose maligne primitive de l'estomac, *Bull Assoc franç p l'etude du cancer* **26** 348, 1937.

306 Lincke, J. Ueber isolierte Lymphogranulomatose des Dunndarmes, *Zentralbl f allg Path u path Anat* **68** 85, 1937.

307 Redish, J. Hodgkin's Disease of the Stomach with Fatal Gastric Hemorrhage, *Arch Path* **23** 844 (June) 1937.

308 Middleton, W. S. Some Clinical Caprices of Hodgkin's Disease, *Ann Int Med* **11** 448, 1937.

tinal lymphadenopathy, involvement of the lung and pleura, constitutional manifestations (general weakness, symptoms of focal infection, tuberculosis, undulant fever and alternating pyrexia), anemia, polymorphonuclear leukocytosis, leukopenia and concurrent tuberculosis

Diagnosis by means of lymph node puncture was used by Estrada,³⁰⁹ Vendeuvre, Ingelrans and Nigoul,³¹⁰ and Weil³¹¹ Barasciutti³¹² found sternal puncture of slight value Wurm³¹³ and van Rooyen³¹⁴ studied the Gordon test clinically but did not note absolute specificity Turner and Jackson³¹⁵ found that eosinophils of normal persons produced a positive reaction to the Gordon test in animals and that the test showed a positive reaction in Hodgkin's disease in proportion to the number of eosinophils present The authors suggested that the agent which produces paralysis is derived from the eosinophils

Stalker, Schlotthauer and Feldman³¹⁶ noted a lesion in a dog which showed the gross and microscopic characteristics of Hodgkin's disease This is apparently rare in animals

Lutzow-Holm³¹⁷ and Mannucci³¹⁸ speculated on the relation of Hodgkin's disease and tuberculosis The former found no connection between the two Muller³¹⁹ was able to trace the origin, or at least the discovery of the disease, to trauma

Lymphosarcoma may also give symptoms because of localization or predominance of the growth in one region In the case reported

309 Estrada, A La citopuntura ganglionare nella linfogranulomatosi maligna del punto di vista diagnostico, *Haematologica* **18** 499, 1937

310 Vendeuvre, A, Ingelrans, P, and Nigoul A propos du diagnostic de la maladie de Hodgkin par la ponction ganglionaire, *Echo méd du Nord* **8** 358, 1937

311 Weil, P E Diagnosis of Hodgkin's Disease by Puncture of Lymph Nodes, *Nord med tidskr* **14** 1262, 1937

312 Barasciutti, A Sulla scarsa utilità della sternopuntura come mezzo diagnostico nel granuloma maligno, *Diag e tec di lab* **8** 481, 1937

313 Wurm, K Ueber den Gordon-Test bei Lymphogranulomatose und seine praktische Bedeutung, *Deutsches Arch f klin Med* **181** 90, 1937

314 van Rooyen, C E Interpretation and Significance of Gordon's Test in Diagnosis of Hodgkin's Disease A Study of One Hundred Cases, *Edinburgh M J* **44** 455, 1937

315 Turner, J C, and Jackson, H, Jr The Etiological Relationship of the Eosinophile to the Gordon Test for Hodgkin's Disease, *J Clin Investigation* **16** 657, 1937

316 Stalker, L K, Schlotthauer, C F, and Feldman, W H Probable Hodgkin's Disease in a Dog Report of a Case, *Am J Cancer* **28** 595, 1936

317 Lutzow-Holm, G Investigations on the Etiology of Lymphogranulomatosis, Especially the Relation Between Lymphogranulomatosis and Tuberculosis, *Norsk mag f lægevidensk* **98**.695, 1937

318 Mannucci, P Granuloma maligno e tubercolosi, *Bollettino* **11**·235, 1937

319 Muller, K Lymphogranulomatose und Trauma, *Med Welt* **11** 852, 1937

by Cruchet and Dupin³²⁰ there was abdominal involvement, with jaundice, in Venable's³²¹ case the condition was primary in the stomach, gastrointestinal perforation of the neoplasm marked Davis'³²² case, Leveuf and Godard³²³ noted involvement of the small intestine in a child, in Cabot case 23111³²⁴ the ileum was involved, in the case reported by Brodin, Lardennois and Tédesco³²⁵ the jejunum was involved, in the 4 cases reported by Collins and Carmody³²⁶ there was gastric involvement, and in the case reported by Keys and Walther³²⁷ the condition simulated duodenal ulcer Zaph, Olin and Kirshbaum³²⁸ have reviewed the clinical and roentgenologic aspects of lymphosarcoma of the stomach

Reifenstein³²⁹ described 2 patients, a man of 42 and a woman of 53 years, in whom looseness of the stools was a feature Lymphosarcoma was demonstrated in both cases at autopsy There was roentgen evidence of abnormality in the first case but not in the second In the man the main involvement was in the stomach, but in the woman the duodenum, jejunum and ileum were involved In a case described by Golub,³³⁰ massive lymphosarcoma of the stomach with ulceration was demonstrated at autopsy The symptoms in this case (a man aged 45 years) were those of the symptom complex of duodenal ulcer with negligible loss of weight and indefinite roentgenologic signs

320 Cruchet, R, and Dupin Lymphosarcomatose abdominale avec ictère, *J de méd de Bordeaux* **114** 168, 1937

321 Venable, D R Primary Lymphosarcoma of Stomach, with Report of a Case, *Texas State J Med* **33** 327, 1937

322 Davis, E Lymphosarcoma with Perforation of Gastric and Intestinal New Growth, *Brit M J* **2** 64, 1937

323 Leveuf, J, and Godard, H Les sarcomes cavitaires de l'intestin grêle chez l'enfant, *Ann d'anat path* **18** 1067, 1936

324 Lymphosarcoma of the Ileum, Cabot Case 23111, *New England J Med* **216** 471, 1937

325 Brodin, P, Lardennois, G, and Tedesco, B Lymphosarcome du jejunum, *Arch d mal de l'app digestif* **27** 447, 1937

326 Collins, E M, and Carmody, M G Lymphosarcoma of Stomach Study of Four Cases, *Am J Digest Dis & Nutrition* **3** 884, 1937

327 Keys, S, and Walther, W W Lymphosarcoma Simulating Duodenal Ulcer, *Lancet* **1** 1169, 1937

328 Zaph, S D, Olin, H A, and Kirshbaum, J D Lymphosarcoma of Stomach Clinical and Roentgenological Aspects, Review of Recent Literature Report of a Case, *Am J Surg* **36** 476, 1937

329 Reifenshtein, E C Lymphosarcoma of the Gastrointestinal Tract, *Rev Gastroenterol* **4** 82, 1937

330 Golub, M Lymphosarcoma of the Stomach with Pain-Food-Ease Rhythm of Three Months Duration, *Rev Gastroenterol* **4** 228, 1937

Hirsch³³¹ described a primary lymphosarcoma of the liver in a man aged 32 years. The clinical symptoms were severe secondary anemia and slight jaundice. The leukocyte count ranged from 6,900 to 9,850 per cubic millimeter, with 51 to 61 per cent lymphocytes. The lymphosarcoma cells infiltrated the walls of large and small branches of the portal vein, with mural thrombi and emboli. Extensive metastases to the bone marrow replaced the normal hemopoietic tissue (myelophthisic anemia). The only other report of a similar case which Hirsch found in the literature was that by Carl Sternberg in 1934.

The genital tract was the seat of involvement in several cases, as follows: the ovary (Durfee, Clark and Peers³³²), the vulva and clitoris (Taussig³³³) and the ovary and uterus (Fornero³³⁴). In Squires'³³⁵ case the cutaneous manifestation was the outstanding feature, in Judson's³³⁶ case the breast was chiefly involved, in Métivier's³³⁷ case the eyelid and in Cabot case 23091³³⁸ the retroperitoneal lymph nodes.

LEUKEMIA

Classification, Incidence—Forkner³³⁹ presented a classification of leukemia (leukosis or leukocythemia) which included the following groups: neutrophilocytic leukemia, eosinophilocytic leukemia, basophilocytic leukemia, chloroleukemia, erythroleukemia, megakaryocytic leukemia, lymphocytic leukemia, leukosarcoma, stem cell leukemia, plasma cell leukemia and monocytic leukemia.

In the report of the Metropolitan Life Insurance Company⁵¹ for the period from 1921 to 1935, it was stated that there were 4,333 deaths from leukemia, 0.21 per cent of the total number of deaths, constituting 1.8 per hundred thousand. The rate for white men (per hundred thousand deaths) was 2, for white women, 1.7, for Negroes, 1.3, and for Negroes, 1.1.

331 Hirsch, E. F. Primary Lymphosarcoma of the Liver with Metastases to the Marrow and Secondary Anemia, *Arch. Path.* **23**: 674 (May) 1937.

332 Durfee, H. A., Clark, B. F., and Peers, J. H. Primary Lymphosarcoma of the Ovary. Report of a Case, *Am. J. Cancer* **30**: 567, 1937.

333 Taussig, F. J. Sarcoma of Vulva, *Am. J. Obst. & Gynec.* **33**: 1017, 1937.

334 Fornero, A. Su di una linfo-sarcomatosi genito-intestinale, a sviluppo simultaneo (ovaie-utero-intestino), *Arch. ital. di anat. e istol. pat.* **7**: 419, 1936.

335 Squires, J. B. Case of Lymphosarcoma Cutis, *J. Med.* **18**: 194, 1937.

336 Judson, H. A. Simultaneous Lymphosarcomatosis and Carcinoma of the Breast in the Same Individual. Case Report, *Radiology* **29**: 578, 1937.

337 Métivier, V. M. Lymphosarcoma of the Eyelid, *Brit. J. Ophth.* **21**: 202, 1937.

338 Retroperitoneal Lymphosarcoma, Cabot Case 23091, *New England J. Med.* **216**: 389, 1937.

339 Forkner, C. E. Classification and Terminology of Leukemia and Allied Disorders, *Arch. Int. Med.* **60**: 582 (Oct.) 1937.

Saxl³⁴⁰ observed leukemia in 5 nurslings. One patient showed signs of anemia and subleukemia practically from birth, others were 6 weeks, 4½ months and 8 months old (showing chloroma, "leukemic myelocytoma or lymphocytoma"). Two had syphilitic mothers. One of these infants, as well as a boy aged 10, died of ileus caused by the leukemic infiltration. Temporary improvement of symptoms with roentgen treatment was obtained in 1 case.

Etiologic Factors—Weil and Bousser³⁴¹ have analyzed 38 cases of leukemia and traumatism. In some cases leukemia was first noted after the trauma. In these cases, the past history was important in suggesting preexistence of the disease. On the other hand, trauma may aggravate or accelerate the leukemic process, or the hemorrhagic tendency may be an important factor. This must be kept in mind when surgical intervention is indicated. It is not possible to demonstrate absolutely a causative relation between leukemia and trauma. This is often a medicolegal problem. It is important, of course, to know the exact status of the patient before the accident, the chronologic relation, the duration of the interval before the leukemia develops and the character and the variety of the leukemia.

Sabrazès and Bideau³⁴² reported the case of a machinist aged 20 years who was exposed to oil for three years. He had myelogenous leukemia, with splenomegaly and slight lymphadenopathy. A causative relation between benzene-containing oils and the leukemia was suggested by the authors.

Acute fatal myeloblastic anemia was noted in a woman aged 55 by Adelheim³⁴³ after malarial treatment of dementia paralytica. While the author said he believed that the malaria caused the leukemia and the exacerbation of the splenomegaly, it is possible that the disease may have been present before the treatment was begun.

Familial and Hereditary Aspects—From a study of the pedigrees of 33 patients, Ardashnikov³⁴⁴ concluded that leukemia is not contagious but that hereditary factors may play a part. The type of inheritance, especially in lymphatic leukemia, is a conditionally dominant autosomal type, with phenotype variation due to other genes or environ-

340 Saxl, O. Zur Frage der Leukämie im Säuglingsalter, *Jahrb f Kinderh* **150** 228, 1937.

341 Weil, P. E., and Bousser, J. Leucémie et traumatisme, *Ann de med* **40** 222, 1936.

342 Sabrazès, J., and Bideau, J., cited in *Chronic Myelogenous Leukemia in Machinery Oilers*, Foreign Letter (Paris), *J A M A* **109** 1376 (Oct 23) 1937.

343 Adelheim, R. Akute Myeloblastenleukämie nach Impfmalaria bei progressiver Paralyse, *München med Wchnschr* **84** 889, 1937.

344 Ardashnikov, S. N. Genetics of Leukæmia in Man, *J Hyg* **37** 286, 1937.

mental factors A relation between myelogenous and lymphatic leukemia is postulated from the occurrence of these diseases in different members of a family

Other aspects of the familial and hereditary features have been analyzed by MacDowell³⁴⁵ in mice and by Morawitz³⁴⁶ and Wullenweber³⁴⁷ Kellett³⁴⁸ noted acute leukemia in 1 of identical twins

Symptomatology and Course—Olmer and Boudouresques³⁴⁹ concluded that the fever in leukemia arises either from infection or from metabolic disturbance They said that the changes in both acute and chronic leukemia are of degree and represent an expression of the same process

Penati³⁵⁰ described a form of acute leukemia in which a complete remission develops, followed by recurrence within six to eight months The initial period is characterized by hyperchromic anemia, thrombopenia, leukopenia, agranulocytosis and the presence of immature cells

Levy, Grand and Krakauer³⁵¹ reported on a patient who presented the difficult problem of the coincidental occurrence of lymphatic leukemia and pertussis Persistent hyperleukocytosis in pertussis suggests follow-up studies for the possibility of leukemia

The effect of infection (bronchopneumonia) was studied in 4 cases of leukemia by Dreyfuss³⁵² The reaction depended on the degree of differentiation of the leukemic cells, with abscesses in 1 case containing polymorphonuclears, and proliferating cells of leukemia and histiocytes in the 3 others The mesenchyma of the lung is frequently involved, with growth around the vessels, bronchi, nodules and alveolar septums Histiocytic alveolitis may be present

345 MacDowell, E C Genetics of Mouse Leukemia, Cancer Probl, Symposium, 1937, p 42, J Hered **28**:131, 1937

346 Morawitz, P Erblichkeit, Rassenhygiene und Bevölkerungspolitik Erbliche und konstitutionelle Faktoren bei einigen Blutkrankheiten, Munchen med Wchnschr **83**:2073, 1936

347 Wullenweber, G Ueber familiäre Leukämie, Deutsche med Wchnschr **63** 488, 1937

348 Kellett, C E Acute Myeloid Leukæmia in One of Identical Twins, Arch Dis Childhood **12** 239, 1937

349 Olmer, J, and Boudouresques, J La fièvre dans la leucémie myéloïde, les formes intermédiaires entre la leucémie myéloïde et la leucémie aiguë, Ann de med **41** 265, 1937

350 Penati, F Leucemie acute e subacute con prestadio amielico e remissione, Minerva med **1** 627, 1937

351 Levy, W, Grand, M J H, and Krakauer, S A Lymphatic Leucemia with Pertussis, J Pediat **10** 781, 1937

352 Dreyfuss, M Le reazioni infiammatorie dei leucemici in base allo studio della broncopolmonite in leucemia, Gior di clin med **18** 965, 1937

Cases of leukemia during the course of pregnancy have been described by Brandstrup,³⁵³ Pontoni,³⁵⁴ Mehta³⁵⁵ and Zanela³⁵⁶. Mention has been made of such special features as gastric involvement (Temlin³⁵⁷), mammary changes (Haram³⁵⁸), changes in the cardiac valves (Koberle³⁵⁹) and auricular involvement (Kindler³⁶⁰) and involvement of the cardiovascular system and brain (Tedeschi³⁶¹).

Connor³⁶² reported osseous changes in 2 cases of lymphatic leukemia in children. In the first case (an aleukemic lymphatic type) there was involvement of all the bones of the arms, legs, many ribs, skull and pelvis. In the second case the bones of the extremities showed the most abnormality. The roentgenographic changes consisted of rarefying processes in the medulla and cortex and lifting of the periosteum, with new bone formation of a fine lace-work type. There was irregular mottling of the skull, pelvis, femurs, tibiae and fibulae, with reduplication of the cortices. A line of transparent tissue, evident between the true cortex and the newly formed bone, indicated infiltration of the soft tissue.

Osseous lesions were also described by Lukowski and Gelman³⁶³ and by Munk and Nauta³⁶⁴.

353 Brandstrup, E. Leukaemia in Pregnancy, *Acta obst et gynec Scand* **17** 284, 1937.

354 Pontoni, L. Reazione mieloide in corso di gravidanza, *Minerva med* **1** 415, 1937.

355 Mehta, C. Case of Acute Lymphatic Leukemia in Pregnancy, *J Obst & Gynaec Brit Emp* **44** 328, 1937.

356 Zanela, S. Myelosis leucaemica und Chloromyelosis leucaemica in graviditate. Beitrag zur Frage der Leukämie und Schwangerschaft, *Zentralbl f Gynak* **61** 763, 1937.

357 Temlin, H. Ueber Beteiligung des Magens bei leukämischen und aleukämischen Erkrankungen, *Wien klin Wchnschr* **50** 1268, 1937.

358 Haram, B. J. Lymphatic Leukaemia with Bilateral Mammary Changes, *Lancet* **1** 1277, 1937.

359 Koberle, F. Ueber leukämische Infiltrate in den Herzklappen, *Ztschr f Kreislaufforsch* **29** 785, 1937.

360 Kindler, W. Ohrmuschelerkrankung und Leukämie, *Ztschr f Hals-, Nasen- u Ohrenh* **41** 427, 1937.

361 Tedeschi, C. Appunti per la istologia patologica delle leucemie, *Boll d Soc med-chir di Modena* **35** 373, 1935.

362 Connor, C. L. Clinically Demonstrable Bone Changes in Leukemia, *Am J Cancer* **29** 20, 1937.

363 Lukowski, L., and Gelman, G. Case of Acute Lymphatic Leukemia with Paradoxical Blood Picture and Extensive Changes in Bones in Child Twelve Years Old, *Polska gaz lek* **16** 724, 1937.

364 Munk, J., and Nauta, J. H. Acute Lymphatic Leukemia with Skeletal Changes, *Maandschr v kindergeneesk* **6** 407, 1937.

Renal complications were noted by Procházka and Vacek,³⁶⁵ and prostatic symptoms were described by Jacobi, Panoff and Herzlich³⁶⁶

Leukemia or a leukemoid blood picture is occasionally noted in neoplastic conditions such as carcinoma of the breast (Sala and Stein³⁶⁷) or of the larynx (Denoyer³⁶⁸) or with other forms of carcinoma (Penzold³⁶⁹)

Tumor formation during the course of leukemia may be the outstanding feature and may lead to an erroneous diagnosis of medullary carcinoma or of neoplasm of the breast, as in the cases described by Fleischhacker and Seyfried³⁷⁰

In von Bonsdorff's³⁷¹ case of atypical leukosis there were multiple tumor-like growths Held and Kieve³⁷² described a patient with retrobulbar and uterine leukemic masses The disease ran an aleukemic course, with 8,800 leukocytes per cubic millimeter, 19 per cent of which were monocytoid myeloblasts

Involvement of the Central Nervous System—Changes in the central nervous system in leukemia were noted by Gordin³⁷³ to include hemorrhages, leukemic changes in the blood vessels and infiltration with specific leukemic tissue A fourth condition, myelomalacia due to pressure from an epidural tumor, was noted in 1 of his cases Leukemic changes in the meninges, cranial nerves and spinal roots were present in some cases The simultaneous existence of leukemia and glioma was noted in 1 case

Scheinker³⁷⁴ noted leukemic infiltrations in the root bundles and spinal ganglions of a patient dying of lymphatic leukemia These

365 Procházka, F, and Vacek, V Case of Myelogenous Leukemia with Infiltration of Kidney, *Časop lék česk* **76** 1413, 1937

366 Jacobi, M, Panoff, C E, and Herzlich, J Leukemic Infiltration of Prostate, *J Urol* **38** 494, 1937

367 Sala, A M, and Stein, R J Carcinoma of the Breast with a Condition of Blood Simulating Chronic Lymphatic Leukemia, *Arch Path* **23** 531 (April) 1937

368 Denoyer, A Carcinoma laringeo in leucemico, *Ann di laring, otol* **36** 185, 1936

369 Penzold, H Leukämie und Carcinom, *Deutsches Arch f klin Med* **180** 430, 1937

370 Fleischhacker, H, and Seyfried, H Ueber Leukämien mit tumorartigem Wachstum, *Wien Arch f inn Med* **30** 177, 1937

371 von Bonsdorff, B Ein Fall von atypischer Leukose mit multiplen, tumorähnlichen Wucherungen, *Folia haemat* **56** 426, 1937

372 Held, E, and Kieve, P Leucémie myeloïde aiguë avec "tumeurs" retrobulbaire et cervicale, *Helvet med acta* **4** 371, 1937

373 Gordin, R Changes in the Central Nervous System in Leukosis, *Finska lak-sällsk. handl* **79** 889, 1936

374 Scheinker, I Zur Pathogenese des Herpes zoster bei lymphatischer Leukämie, *Wien klin Wchnschr* **50** 1065, 1937

changes were suggested as a cause of the hemorrhagic herpes present during the course of the disease

Reviewing the literature on neurologic changes in leukemia, Minkenhof³⁷⁵ added another case of subacute lymphatic leukemia which simulated meningococcic sepsis with meningitis

Cutaneous Manifestations in Leukemia—The cutaneous manifestations of leukemia have received attention from numerous authors. In addition to those cited, features of the cutaneous lesions have been described by Lapiere and Compere,³⁷⁶ Weil,³⁷⁷ Pautrier,³⁷⁸ Hitch and Smith,³⁷⁹ Gattwinkel,³⁸⁰ Kwiatkowski,³⁸¹ Babonneix and Gisselbrecht,³⁸² Scheinker,³⁷⁴ Lutz,³⁸³ Nekam,³⁸⁴ Florentin and Picard,³⁸⁵ Gottron,³⁸⁶ Nomland,³⁸⁷ Sirota and Kuznets,³⁸⁸ and Brau³⁸⁹

375 Minkenhof, J E. Meningism in Leukemia and in Weil's Disease, *Nederl tijdschr v geneesk* **81** 4448, 1937

376 Lapiere, S, and Compere. Leucemie aigüe a cellules indifférenciées, accompagnée de leucémides cutanées spécifiques mais éphémères, à type de roseole papuleuse, *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1269, 1937

377 Weil, P E. Manifestations cutanées des leucémies et des granulomatoses, *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1209, 1937

378 Pautrier, L M. Erythrodermie quasi généralisée, mais respectant des îlots de peau saine, avec petites tumeurs à formule histologique de mycosis fungoïde, et s'accompagnant de lésions sanguines du type leucémie lymphoïde (leucocytose à 120,000 et 85 per cent de lymphocytes), *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1307, 1937

379 Hitch, J M, and Smith, D C. Lymphatic Leukemia. Report of a Case Apparently Limited to the Skin, Superficial Lymphatic Glands and Blood Stream, *Arch Dermat & Syph* **36** 1 (July) 1937

380 Gattwinkel. Leukämie der Haut und Erythrodermie, *Arch f Dermat u Syph* **175** 578, 1937

381 Kwiatkowski, E L. Sur un cas de lymphadenose cutanée "latente" accompagnée de lésions atrophiques et dyschromiques de la peau du membre supérieur gauche, d'origine spinale, probablement leucémique, *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1217, 1937

382 Babonneix, L, and Gisselbrecht. Sur un cas de leucémie lymphoïde avec leucémides, *Gaz d hôp* **110** 816, 1937

383 Lutz, W. Erythrodermie exfoliante généralisée, primaire, idiopathique, évoluant ultérieurement en erythrodermie leucémique (la peau comme lieu d'origine de la leucémie), *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1230, 1937

384 Nekam, L. Les manifestations cutanées de la leucémie myeloïde, *Bull Soc franç de dermat et syph (Reunion dermat, Strasbourg)* **44** 1236, 1937

385 Florentin, G J, and Picard, D. La forme hémorragique de la myelose aleucémique megacaryocytaire, *Bull et mem Soc med d hôp de Paris* **53** 1061, 1937

386 Gottron, H. Zur Leukämie der Haut, *Med Klin* **33** 373 and 404, 1937

Epstein and MacEachern³⁹⁰ found exfoliative erythroderma in 66 per cent of the patients with Hodgkin's disease with cutaneous manifestation. With progress of the disease, the skin became hyperpigmented and inelastic. In the group of cases of lymphoblastoma associated with leukemia the following types of cutaneous lesions were noted: (a) specific lesions, (b) toxic manifestations (lymphoblastomids or leukemids) and (c) accidentally associated lesions. Metastatic nodules of lymphosarcoma and shotty nodules of the face and upper extremities of myelogenous leukemia are characteristic.

Ferreira Marques³⁹¹ described the case of a man aged 76 with chronic lymphatic leukemia who had herpes zoster involving the whole trunk. In only 3 of 42 cases of leukemia with herpes zoster reported in the literature was there the myelogenous type. The maximum incidence was found to be during the second and the third year of the disease and during the age decade between 50 and 60. The disease was most frequent in males. Two cases of facial paralysis and 2 of paralysis of the extremities were noted. Ferreira Marques said he felt that the leukemic herpes zoster is a virus manifestation.

In 3 cases of lymphomatosis with cutaneous manifestations, reported by Gaté and Cuilleret,³⁹² the leukemic nature was shown by blood examination, biopsy and clinically (lymphadenopathy, splenomegaly and hepatomegaly).

The cutaneous lesions in monocytic leukemia were emphasized also by Sannicandro³⁹³. The infiltrations were of metastatic origin, with no evidence of the involvement of the local reticuloendothelial system. The lesions include nodules, macular infiltration and cutaneous hemorrhages. This patient, a man of 37, showed enlargement of the liver, spleen and peripheral lymph nodes.

Montgomery and Watkins³⁹⁴ described 5 cases of monocytic leukemia with cutaneous manifestations. These varied from discrete necrotic

387 Nomland, R. Skin Changes in Leukemia, *J Iowa M Soc* **27** 25, 1937

388 Sirota, L. S., and Kuznets, M. Pour la clinique et l'histologie de la leucémie lymphatique, *Ann de dermat et syph* **7** 1113, 1936

389 Brau, J. G. Myeloid Leukemia Manifested by Skin Infiltration, *Dallas M J* **22** 121, 1936

390 Epstein, E., and MacEachern, K. Dermatologic Manifestations of the Lymphoblastoma-Leukemia Group, *Arch Int Med* **60** 867 (Nov) 1937

391 Marques, J. F. Herpes zoster generalisatus bei Leukämie, *Arch f Dermat u Syph* **176** 295, 1937

392 Gate, J., and Cuilleret, P. A propos des manifestations cutanées des leucémies, *J de méd de Lyon* **18** 299, 1937

393 Sannicandro, G. Le manifestazioni cutanee della leucemia monocitica, *Arch ital di dermat, sif* **13** 263, 1937

394 Montgomery, H., and Watkins, C. H. Monocytic Leukemia. Cutaneous Manifestations of the Naegeli and Schilling Types, *Hemocytologic Differentiation*, *Arch Int Med* **60** 51 (July) 1937

nodules or purpuric lesions to generalized exfoliative dermatitis. Two types of monocytic leukemia are differentiated—the Naegeli type (myelogenous leukemia with a predominance of monocytes) and the Schilling type (leukemic reticuloendotheliosis). In the latter type there is a distinctive histopathologic picture, evident also on direct examination of the skin. The authors concluded that myelogenous leukemia may terminate in monocytic leukemia or that the lymphatic type may change to the monocytic type. There may be acute, chronic and aleukemic forms of the Schilling type. Temporary regression of the lesions may be produced with roentgen rays and local applications (pruritis or secondary infections), or arsenic or fever therapy may be tried.

Leukemia and Tuberculosis—In the case reported by Ryan and Medlar,³⁹⁵ advanced tuberculosis and lymphatic leukemia were present. Although a high lymphocyte count is usually considered of advantage in tuberculosis, the authors concluded that leukemic lymphocytes are abnormal in function.

Lukeš,³⁹⁶ noting the occasional favorable influence of intercurrent infections on the course of chronic myelogenous leukemia, injected 0.1 mg of Calmette vaccine intravenously. There was a decrease in the leukocyte count and a fall in the number of primitive cells.

Mills and Townsend³⁹⁷ reported 2 cases of acute generalized tuberculosis, the blood resembling that of patients with acute myeloblastic leukemia. At autopsy the tissues were not typical of those in leukemia, however, and it was suggested that the condition may have been due to the tuberculosis.

In sensitized tuberculous rabbits, Feldman and Stasney³⁹⁸ reproduced the leukemoid blood picture sometimes noted in tuberculous patients, by the injection of tuberculin. Leukocyte counts (granulocytes) of 9,000 to 48,000 rose to 42,000 to 124,000 per cubic millimeter in from twenty-four to seventy-two hours. There was marked bone marrow activity (hyperplasia and increased mitosis), but the monocytes and lymphocytes did not take part in the reaction. This leukemoid response was not elicited in nontuberculous rabbits.

395 Ryan, W. J., and Medlar, E. M. Coexistence of Lymphocytic Leukaemia and Far-Advanced Pulmonary Tuberculosis. Report of Case, *Am Rev Tuberc* **36** 212, 1937.

396 Lukeš, J. Myeloleucemie chronique et tuberculose, *Časop lek česk* **75** 478, 1936.

397 Mills, E. S., and Townsend, S. R. Leukaemoid Blood Picture in Tuberculosis, *Canad M A J* **37** 56, 1937.

398 Feldman, W. H., and Stasney, J. Leukemoid Response of Tuberculous Rabbits to the Administration of Tuberculin, *Am J M Sc* **193** 28, 1937.

Differential Diagnosis—To differentiate acute leukemia in certain cases from infectious mononucleosis, Ustvedt ²⁴⁴ noted that the characteristic myeloblastic transformation of the bone marrow is easily demonstrable on sternal puncture. In infectious mononucleosis there are fewer cells, and they are of the more normal types.

While the anemia, acute symptoms and gross immaturity of the cells help to differentiate acute leukemia from infectious mononucleosis, Israels ²⁴³ noted that the diagnosis in some cases is more difficult. The pyrexia, splenomegaly and lymphadenopathy may be similar. In 1 case of infectious mononucleosis, hemorrhage and anemia were present. While the total leukocyte count is not necessarily characteristic, the structure of the cells and the heterophile antibody test are of value.

Abt ³⁹⁹ summarized the conditions in childhood which may simulate leukemia. Of those conditions in which leukocytosis is present, he listed pertussis, pneumonia, sepsis, von Jaksch's pseudoleukemic anemia, Cooley's Mediterranean erythroblastic anemia, infectious mononucleosis, mediastinal tumor and essential lipoid histiocytosis of Niemann and Pick. Among the nonleukemic conditions are sepsis, agranulocytosis, Gaucher's disease, nonlipoid splenohepatomegaly (Letterer-Siwe disease) and malaria. On the other hand, leukemia, with leukocytosis, may simulate mediastinal tumor, rheumatism, diarrhea and parotitis. In the aleukemic states the disease may simulate sepsis, appendicitis and aplastic anemia.

Leukemoid Blood Pictures—A leukemoid blood picture (21,000 leukocytes, with 40 per cent myelocytes and metamyelocytes, normoblasts) was noted in a woman with subchronic arthritis by Totterman ⁴⁰⁰. No change, as would be expected in leukemia, appeared during two years of observation, and the material obtained on sternal puncture was interpreted as showing a nonleukemic state. A similar leukemoid picture was noted in a man with anemia due to *Bothriocephalus* after pneumonia. The immature leukocytes disappeared from the peripheral blood after treatment of the anemia.

Two patients with fibrosis of the bone marrow, studied by Mettier and Rusk, ⁴⁰¹ showed a blood picture simulating that of leukemia. The first patient showed a hemorrhagic tendency and leukopenia, with moderate splenomegaly, while the other had characteristic symptoms of

399 Abt, A. F. Diagnosis of Leukemia in Childhood, *M. Clin. North America* **21** 89, 1937.

400 Totterman, G. On So-Called Myeloid Reaction, *Finska läk-sällsk. handl.* **79** 880, 1936.

401 Mettier, S. R., and Rusk, G. Y. Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture. Report of Two Cases, *Am. J. Path.* **13** 377, 1937.

leukemia The medullary cavities of the bones showed increased fibrosis and a few spicules of bone, with partial obliteration of the hemopoietic tissue No erythrocytic tissue was found in the sinusoids of the liver or spleen The blood of 1 patient suggested the diagnosis of aleukemic myelosis with terminal leukocytosis (myelocytes, 54 per cent), whereas that of the second showed 68,500 leukocytes per cubic millimeter, with 19 per cent myelocytes and 1 per cent blasts A few days before death occurred examination showed 62 per cent myeloblasts after much roentgen therapy

Types—A case of aleukemic plasma cell leukemia in a 66 year old woman was reported by Reiter and Freeman⁴⁰² Symptoms included weakness, a tingling sensation in the fingers and difficulty in walking, simulating the symptoms of pernicious anemia Although no plasma cells were reported in the peripheral blood, the tissues, especially of the liver and spleen, showed extensive infiltration at autopsy No tumor was noted Both plasmoblasts and plasmocytes were present

Ten male and 5 female patients with lymphosarcoma cell leukemia were described by Isaacs⁴⁰³ The lymphosarcoma cell, present in from 4 to 98 per cent, is characterized by a large nucleolus, which in films stained with Wright's stain and brilliant cresyl blue is surrounded by a deeply staining wall of chromatin The leukemic phase is ushered in with an exacerbation of symptoms and fever Leukocytosis (23,000 to 156,000 cells per cubic millimeter) may be present, with progressive anemia and thrombopenia Relapses and remissions are noted The average duration of the leukemic phase is less than two months, although 1 patient lived at least seven years Cooley and Hanske⁴⁰⁴ described a case of acute lymphatic leukemia associated with lymphosarcoma

Jordan⁴⁰⁵ described the blood and tissues of an 18 year old girl who died of acute hemoblastic leukemia The predominant cell resembled the small lymphocyte, which Jordan said represented a primitive cell type This is the type of cell called by others a myeloblast, micro-myeloblast, primitive blast and lymphoidocyte There was gross invasion or transformation of the bone marrow, spleen, lymph nodes and thymus, with infiltration into other organs

402 Reiter, B R, and Freeman, J I Plasma Cell Leukemia, *Am J M Sc* **193** 38, 1937

403 Isaacs, R Lymphosarcoma Cell Leukemia, *Ann Int Med* **11** 657, 1937

404 Cooley, L E, and Hanske, E A Acute Lymphatic Leukemia, *J Iowa M Soc* **27** 535, 1937

405 Jordan, H E Hemoblastic Leukemia Study of a Case, *Arch Path* **23** 653 (May) 1937

Isaacs and Sturgis ⁴⁰⁶ studied 33 patients with monocytic leukemia. Of these, 70 per cent were males. The ages ranged from 5 to 78 years, with 59 per cent of the patients over 50. Acute and chronic forms were noted, with one to three relapses and remissions. In 1 case monocytic chloroma developed. The symptoms and signs in order of frequency were: weakness, 100 per cent, clinical splenomegaly, 82 per cent (8 patients who came to autopsy showed splenomegaly), fever, 82 per cent, loss of weight, 77 per cent, oral lesions (cheek, gums and pharynx), 73 per cent, pain, 64 per cent, hepatomegaly, 59 per cent, albuminuria at some stage, 50 per cent, purpura, 41 per cent, enlargement of the cervical glands (usually mild), 41 per cent, cutaneous lesions (other than purpura), 36 per cent, and epistaxis, 36 per cent. Characteristic changes were noted in the blood. Blood transfusion and arsenic gave temporary symptomatic remissions, irradiation was not efficient.

Osgood ⁴⁰⁷ reported data on 6 cases of monocytic leukemia and tabulated material for 127 cases reported in the literature. The clinical features were summarized as follows: an acute course, an unusual tendency toward swelling of the gums and the frequent association of fever, stomatitis and hemorrhages. The hematologic characteristics were the appearance of "promonocytes" in the blood and monoblasts and "promonocytes" in the sternal marrow. A specific cutaneous lesion was described. Wainright and Duff ⁴⁰⁸ published a detailed study of a case of acute monocytic leukemia in a 40 year old woman, with both myeloid and monocytic response.

Kandel ⁴⁰⁹ found reports of 175 cases of chloroma in the literature and noted that in most of the recent cases the chloroma had been classed as myeloid instead of lymphatic. It was postulated that chloroma is simply a variant of myelogenous leukemia in which the myeloblast develops into an invasive neoplasm.

Roehm, Riker and Olsen ⁴¹⁰ described the occurrence of chloroma in a girl aged 13 years. The blood was aleukemic until nine days before death, and no abnormal leukocytes were noted in the blood stream. Profound anemia was present. The tumor cell, at autopsy, showed a

⁴⁰⁶ Isaacs, R., and Sturgis, C. C. Types of Monocytic Leukemia, *Tr. A. Am. Physicians* **51** 40, 1936.

⁴⁰⁷ Osgood, E. E. Monocytic Leukemia. Report of Six Cases and Review of One Hundred and Twenty-Seven Cases, *Arch. Int. Med.* **59** 931 (June) 1937.

⁴⁰⁸ Wainright, C. W., and Duff, G. L. Monocytic Leukemia, *Bull. Johns Hopkins Hosp.* **58**:267, 1936.

⁴⁰⁹ Kandel, E. V. Chloroma. Review of the Literature from 1926 to 1936 and Report of Three Cases, *Arch. Int. Med.* **59**:691 (April) 1937.

⁴¹⁰ Roehm, H. R., Riker, A., and Olsen, R. E. Chloroma. Report of a Case, *Ann. Int. Med.* **10** 1054, 1937.

negative reaction for oxidase. There was extensive involvement of the cranium and viscera. The authors concluded that the green pigmentation was due to phagocytosis of blood in the obstructed capillaries by endothelial cells.

Forkner, Teng, Ch'u and Cochran⁴¹¹ reported the fifth case of acute eosinophilic leukemia recorded in the literature. The average age of onset is 35.5 years (17 to 45) with a duration of twelve days to three months. The authors found that significant enlargement of lymph nodes was more common in this type than in other forms of myelogenous leukemia and that gross immaturity of the cells was not so marked.

Pathology and Pathologic Physiology—Beltrametti, Rettanni and Bascapè⁴¹² concluded that the anemia of leukemia is hemolytic and is a function of the hyperactivity of the spleen. In 12 cases (myelogenous and lymphatic leukemia) they noted a reduction in the number of leukocytes after irradiation, with an increase in the number of red blood cells, a lessening of the dispersion in the size of the red blood cells and a decrease in the evidence of destruction of hemoglobin.

Allen and Dickey⁴¹³ studied the secretion of polymorphonuclear neutrophils into the saliva in 10 cases of chronic myelogenous leukemia before and after roentgen therapy. An increase in the number of cells in the saliva follows maturation of myelocytes into forms capable of leukopenesis. The authors said they favored the view that irradiation increases the degree of maturation of the cells, although under certain circumstances it may cause the death of some of the abnormal forms. Irradiation may lower the blood stream and gastrointestinal threshold for leukopenesis.

Strumia and Boerner⁴¹⁴ studied the phagocytic activity of leukemic cells toward *Staphylococcus aureus haemolyticus* in vitro. None of the cells of the lymphocyte series showed phagocytic activity. In myelogenous leukemia, hemocytoblasts and myeloblasts showed but slight or doubtful phagocytic activity, but metamyelocytes, rod nuclear cells and adult neutrophils showed active phagocytosis. Turk cells showed no phagocytic activity. Monoblasts showed slight activity, hemohistioblastic cells showed strong phagocytic activity. The lymphoid cells of

411 Forkner, C. E., Teng, C. T., Ch'u, Y.-C., and Cochran, W. Eosinophilic or Eosinophilic Myelogenous Leukemia, *Chinese M. J.* **51** 609, 1937.

412 Beltrametti, L., Rettanni, G., and Bascapè, A. L'anemia nelle leucemie, *Haematologica* **18** 337, 1937.

413 Allen, K. D. A., and Dickey, L. The Saliva Cell Count in Myelogenous Leukemia, *Am. J. Roentgenol.* **38** 57, 1937.

414 Strumia, M. M., and Boerner, F. Phagocytic Activity of Circulating Cells in the Various Types of Leukemia, *Am. J. Path.* **13** 335, 1937.

infectious mononucleosis showed no phagocytosis. Eosinophils showed activity but less than that of the neutrophils or monocytes. Rieder's cells showed slight but definite activity.

Benians⁴¹⁵ noted that a gel was formed when congo red was mixed with leukemic blood.

In leukemia, Ishikawa⁴¹⁶ found that p_H values for leukocytes were often abnormally high, above the normal of 12.5 to 17.5 (aerobic) and 11 to 12 (anaerobic).

The nucleus of myeloblasts in leukemia, Ishikawa⁴¹⁷ found, had a p_H of 6.5 and the cytoplasm a p_H of 6.4. This was more acid than the neutrophilic leukocytes of healthy men (nucleus p_H , 6.7, cytoplasm p_H , 6.6, granules, 7.1). While lymphocytes and monocytes had an acid reaction, eosinophilic granules were alkaline (p_H , 7.18).

Bossa⁴¹⁸ noted that leukemic leukocytes, especially of the lymphatic type, have the power of dehydrogenating fatty acids, with the production of keto acids (acetic). Bossa⁴¹⁹ found that the cells in cases of chronic myelogenous leukemia have a higher glycolytic rate than those in cases of lymphatic leukemia. The metabolism of the myeloid cells resembles that of neoplastic tissue, and that of the lymphoid series is more like that of embryonic cells.

The cells of the bone marrow, lymph nodes and circulating blood of patients with lymphatic leukemia were found by Look⁴²⁰ to be without proteolytic action, whereas the marrow and lymph nodes of patients with myelogenous leukemia showed a strong digestive action. Stephens and Hawley⁴²¹ found unusually high values for reduced cevitamic acid in the whole blood of patients with leukemia, owing to the preponderance of leukocytes. Oszacki and Kurzweil⁴²² noted an alkalosis of the blood (p_H , above 7.36) of patients with leukemia, similar to the condition of the blood of patients with neoplastic disease.

415 Benians, T. H. C. Observations on the Action of Congo Red on Normal and Leucemic Blood, *J. Lab. & Clin. Med.* **22** 1246, 1937.

416 Ishikawa, A. The Oxidation-Reduction Potential of Leukocytes (Measured with the Micromanipulator), *Ztschr. f. klin. path. Hamatol.* **4** 403, 1935.

417 Ishikawa, A. The Hydrogen-Ion Concentration of Leukocytes (Determined by Micromanipulators), *Ztschr. f. klin. path. Hamatol.* **4** 305, 1935.

418 Bossa, G. Sul potere deidrogenativo dei leucociti leucemici per gli acidi grassi, *Riforma med.* **53** 1545, 1937.

419 Bossa, G. Sul metabolismo dei leucociti leucemici, *Haematologica* **18** 652, 1937.

420 Look, W. Proteolysen-und Hemmungsversuche bei Agranulocytose-und Leukamieerkrankungen, *Deutsches Arch. f. klin. Med.* **178** 559, 1936.

421 Stephens, D. J., and Hawley, E. E. Partition of Reduced Ascorbic Acid in Blood, *J. Biol. Chem.* **115** 653, 1936.

422 Oszacki, A., and Kurzweil, R. Alkalose des Blutes bei Neoplasmen und ihre diagnostische und pathogenetische Bedeutung, *Biochem. Ztschr.* **289** 234, 1937.

Watson ⁴²³ found that the fecal excretion of urobilinogen was increased above the normal of 40 to 200 mg per day in cases of pernicious anemia, Hodgkin's disease and leukemia

Fiessinger and Laur ⁴²⁴ described the presence of round cytoplasmic particles, 4 to 8 microns in diameter, in the blood of patients with chronic lymphatic or myelogenous leukemia They are probably artefacts, secondary to abnormal cytoplasmic fragility of the leukemic cells Liberti ⁴²⁵ concluded that the nuclear shadows seen in blood films in cases of acute lymphatic leukemia are artefacts Yaguda, ⁴²⁶ in noting the characteristic "patterns" in the cell types of the marrow in the different types of leukemia, pointed out the diagnostic importance of studies of the bone marrow, especially in the aleukemic states

Leukemia in Animals—In irradiated and nonirradiated mice inoculation with tumor cells of myeloid leukemia produced proliferation of the inoculated cells in the spleen, liver, lymph nodes and kidney and leukemic transformation of the marrow, with discharge of immature cells into the blood stream From these experiments Rask-Nielsen and Rask-Nielsen ⁴²⁷ postulated that in mammalian leukemia an agent is present which causes a proliferation of the cells of the marrow

Greppin ⁴²⁸ noted that bile neutralized the virus of fowl leukemia but that the inactivated virus did not produce immunity It was possible to produce some degree of immunity with virus attenuated by heat, but no antibodies (complement deviation) could be demonstrated in the blood

Magat and Magat ⁴²⁹ found that after the injection of lecithin perhydrate into leukemic chickens, there were spectroscopic differences from the blood of normal chickens receiving the same injection or from those with avian plague, diphtheria or acute anemia The reagent was more toxic in leukemic chickens than in the others

423 Watson, C J Studies of Urobilinogen Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of Liver or Biliary Tract, *Arch Int Med* **59** 196 (Feb) 1937

424 Fiessinger, N, and Laur, C M Sur un corpusculin du sang des leucemies, *Ann de méd* **40** 212, 1936

425 Liberti, R Le ombre nucleari nella linfadenia leucemica acuta, *Haematologica* **18** 599, 1937

426 Yaguda, A The Bone Marrow in Leukemia, *J M Soc New Jersey* **33** 705, 1936

427 Rask-Nielsen, H C, and Rask-Nielsen, R Further Investigations on a Transmissible Myeloid Leukosis in White Mice, *Acta path et microbiol Scandinav* **13** 244, 1936

428 Greppin, J Les phenomenes d'immunité dans la leucémie transmissible des poules, *Bull Assoc franç p l'étude du cancer* **26** 232, 1937

429 Magat, I, and Magat, M Recherches spectroscopiques sur le sang de poules leucémiques, *Bull Assoc franç p l'étude du cancer* **26** 259, 1937

Storti and de Filippi⁴³⁰ concluded that the reticuloendothelial system of the host does not take part in the development of leukemia in fowls after inoculation

Using virus of chicken sarcoma, leukosis and osteochondrosarcoma, Furth and Breedis⁴³¹ found that viruses multiply in vitro only in the presence of cells on which they confer neoplastic properties. A single virus may stimulate both primitive blood cells and fibroblast-like cells. Leukemic myeloblasts of chickens remained viable in liquid cultures and were capable of producing leukosis when inoculated into chickens after thirty days. Viruses retained their characteristics during observation for from three to five years.

Furth, Kahn and Breedis⁴³² were able to transmit a type of mouse leukemia by the intravenous injection of single living leukemic cells. Injured cells or noncellular material was not effective in transmitting the disease. These experiments suggest that generalized leukemia may arise from a single focus, as opposed to the concept of multicentric origin.

Barnes and Furth⁴³³ were able to transmit leukemia (atypical cell type) from one mouse to another of the same group or to unrelated mice if the latter had received massive and repeated doses of 1000 röntgen rays. Transmission failed when cell-free material was used or when the cells had been frozen rapidly to minus 30 C. When frozen slowly to minus 70 C. for thirty minutes or when kept at this temperature for thirty-two days, the cells were able to transmit the disease, possibly because some cells escaped uninjured. Sarcoma tissue of mice can be frozen to minus 70 C. and preserved for at least fifty-six days without inactivation (Breedis, Barnes and Furth⁴³⁴).

Treatment—Sgaltzer¹⁶⁶ found that "total irradiation" was effective during the first two years in myelogenous leukemia but that in the later stages it had to be combined with local irradiation over the splenic area. In using the method in lymphatic leukemia, local treatment over

430 Storti, E., and de Filippi, P. Das Verhalten des reticulohistiocytaren Systems bei der Histogenese der ubertragbaren Huhnerleukämie, *Folia haemat* 58 20, 1937

431 Furth, J., and Breedis, C. Attempts at Cultivation of the Viruses Producing Leukosis in Fowls, *Arch Path* 24 281 (Sept.) 1937

432 Furth, J., Kahn, M. C., and Breedis, C. The Transmission of Leukemia of Mice with a Single Cell, *Am J Cancer* 31 276, 1937

433 Barnes, W. A., and Furth, J. Transmissible Leukemia in Mice with Atypical Cells Resembling Megakaryocytes, *Am J Cancer* 30 75, 1937

434 Breedis, C., Barnes, W. A., and Furth, J. Effect of Rate of Freezing on Transmitting Agent of Neoplasms of Mice, *Proc Soc Exper Biol & Med* 36 220, 1937

the spleen and lymph nodes was necessary. This method did not influence the final outcome of the disease, although the course may have been somewhat milder than with the older methods.

Hunter⁴³⁵ said he preferred high voltage roentgen therapy for chronic myelogenous leukemia rather than solution of potassium arsenite U S P. For aleukemic myelogenous leukemia he suggested that high voltage therapy to the spleen is worthy of a trial. In acute myeloblastic leukemia he found that all specific treatment was futile. Roentgen therapy made "the patient worse," and the use of blood transfusions and arsenic preparations should be discouraged, he said, because neither agent produces, with any consistency, even temporary benefit.

Parsons⁴³⁶ reported excellent results in chronic leukemia with splenomegaly with the use of radium. Daily applications for three fifteen hour periods of 250 to 300 mg of radium, screened with 2 mm of lead, were made usually over the spleen once a year. Unpleasant reactions were less severe than after roentgen therapy.

Stephens⁴³⁷ reported the production of hemopoietic and symptomatic remissions in a case of chronic myelogenous leukemia with arsenic and in another with irradiation. In the latter case, therapy was followed by a marked increase in excretion of nitrogen, but there was no change in the nitrogen balance in the former case.

Eley⁴³⁸ found placental extract to be of use in stopping the hemorrhages in leukemia.

The blood of a patient with chronic myelogenous leukemia was used by Bock⁴³⁹ to treat agranulocytosis. Fourteen transfusions were used with successful results. The withdrawal of the blood from the leukemic patient, with replacement with normal blood, was not followed by any harmful sequelae, and the author said it may even have been beneficial.

In the course of the arsenic treatment of chronic myelogenous leukemia, symptoms of arsenic poisoning may develop. Kandel and LeRoy⁴⁴⁰ noted herpes zoster, cirrhosis, keratosis, polyneuritis, erythema, portal fibrosis and ascites. Some patients showed moist rales

435 Hunter, F. T. *The Leukemias: Their Diagnosis, Prognosis and Treatment*, M. Clin. North America **21** 349, 1937.

436 Parsons, C. G. *Radium in Treatment of Leukemia*, Brit. J. Radiol. **10** 573, 1937.

437 Stephens, D. J. *Chronic Myelogenous Leukemia: Observations Before and During Remissions Induced by Solution of Potassium Arsenite and by Roentgen Therapy with Particular Reference to Bone Marrow*, Am. J. M. Sc. **194** 25, 1937.

438 Eley, R. C. *The Clinical Application of Coagulant Substance Obtained from Human Placenta*, J. Michigan State M. Soc. **36** 377, 1937.

439 Bock, H. E. *Die Behandlung der Agranulozytose*, Fortschr. d. Therap. **13** 537, 1937.

440 Kandel, E. V., and Leroy, G. V. *Chronic Arsenical Poisoning During Treatment of Chronic Myeloid Leukemia*, Arch. Int. Med. **60** 846 (Nov.) 1937.

and a chronic cough. The symptoms of conjunctival and nasal congestion and of gastrointestinal disorders may be relatively late features compared with the others in patients who show some degree of toleration for the drug. When keratoses appear the use of arsenic must be discontinued temporarily and cautiously resumed after a rest period. Occasionally it is necessary to resort to roentgen therapy instead. Ordinarily it is well to wait with arsenic therapy until the postirradiation decline in the number of leukocytes has reached its lowest point. Twenty-one day cycles of arsenic, interspersed with twenty-one day rest periods were recommended.

Heimild and Schjødt⁴⁴¹ suggested the use of cevitic acid in acute myeloblastic leukemia and in the chronic lymphatic form. They said they felt that better results were obtained (decrease in leukocyte count and cessation of hemorrhage) when this treatment supplemented roentgen therapy. The results were less marked in chronic myelogenous leukemia.

BONE MARROW

With the increased study of bone marrow, the literature on the subject is becoming more involved. The sternal puncture method appears popular, but it is evident that quantitative data must be viewed with caution, as in some cases "pure" marrow is obtained, whereas in others a weak suspension of some marrow cells in blood is aspirated.

Details of the sternal puncture method of studying bone marrow were reviewed by Vogel, Erf and Rosenthal⁴⁴². They described the appearance of the cells found in health and in disease.

Kirschbaum and Downey⁴⁴³ found that the tissue section is the best method for the study of orientation in bone marrow, but the dry imprint method offers many advantages both for study of the cellular structure and for ease of preparation. Dameshek, Henstell and Valentine⁴⁴⁴ said they preferred the biopsy to the puncture method, but the latter has the advantage of greater technical simplicity.

Stasney and Higgins⁴⁴⁵ compared the cellular content of the bone marrow of the ribs and that of the proximal portion and of the middle

441 Heimild, S, and Schjødt, E. Remission During the Course of Leukemia Treated with Cevitic Acid, *Ugeskr f læger* **98** 1135, 1936

442 Vogel, P, Erf, L. A, and Rosenthal, N. Hematological Observations on Bone Marrow Obtained by Sternal Puncture, *Am J Clin Path* **7** 436, 1937

443 Kirschbaum, A, and Downey, H. A Comparison of Some of the Methods Used in Studies of Hemopoietic Tissues, *Anat Rec* **68** 227, 1937

444 Dameshek, W, Henstell, H. H, and Valentine, E. H. The Comparative Value and the Limitations of the Trepine and Puncture Methods for Biopsy of the Sternal Marrow, *Ann Int Med* **11** 801, 1937

445 Stasney, J, and Higgins, G. M. A Quantitative Cytologic Study of the Bone Marrow of the Adult Dog, *Am J M Sc* **193** 462, 1937

portion of the femurs of 35 dogs, using imprint preparations. A remarkable similarity was noted in all the regions studied, leading to the conclusion that a uniform mechanism regulates hemopoiesis in different portions of the widely distributed marrow. The authors concluded that "the appraisal of the marrow of any one region will reveal what the trend of its cellular changes is elsewhere in the body."

Helpap⁴⁴⁶ criticized the sternal puncture method on the basis that bone marrow is not homogeneous and that samples taken from one part of a bone differ from those taken from another part. He studied the sternal marrow of 32 patients who died as a result of diseases other than blood dyscrasias and found that 22 showed a homogeneous marrow. He found that the marrow of the long bones may differ from that of the sternum.

Isaacs⁴⁴⁷ studied bone marrow obtained for biopsy and autopsy. The cells of the sternal bone marrow of 152 patients with various pathologic conditions and of 11 normal persons were enumerated from measured suspensions in serum. He found a great variation in the number and in the relative predominance of stages in the marrow, depending on the physiologic state of the individual at the moment the specimen was taken. Normally there are from 900,000 to 1,000,000 nucleated cells of all types per cubic millimeter. Of these, 23.1 ± 8 per cent are primitive blasts (erythroblasts and leukoblasts), 3 ± 1 per cent, megaloblasts, 7.2 ± 2.5 per cent, basophilic normoblasts, and 12 ± 7 per cent, eosinophilic normoblasts. In aplastic and hypoplastic anemia (nephropathy) the stage at which inhibition of growth is noted is the primitive blast stage, in pernicious anemia, cirrhosis of the liver and most macrocytic anemias, at the megaloblast stage, and in leukemia and in infection, at the normoblast stage.

The normal myelogram from the blood-diluted material aspirated from the sternum was reported by Mallarmé⁴⁴⁸ as polymorphonuclear neutrophils, 32.5 per cent, polymorphonuclear eosinophils, 2 per cent, polymorphonuclear basophils, 0.04 per cent, metamyelocytic neutrophils, 12 per cent, metamyelocytic eosinophils, 0.5 per cent, promyelocytes, 1.5 per cent, leukoblasts, 2.5 per cent, proerythroblasts and basophilic erythroblasts, 6 per cent, polychromatic and orthochromatic erythroblasts, 10 per cent, megaloblasts and promegaloblasts, 0, lymphocytes and mononuclear cells, 9.5 per cent, monocytes and reticuloendothelial cells, 2.5 per cent, plasmocytes and irritation cells, 0.9 per cent, and megakaryocytes, 0.06 per cent. The granulocyte-erythroblast ratio is

446 Helpap, K. Zur Kritik der Sternalpunktion, *Klin Wchnschr* **16** 558, 1937.

447 Isaacs, R. The Bone Marrow in Anemia. The Red Blood Cells, *Am J M Sc* **193** 181, 1937.

448 Mallarmé, J. Le myélogramme normal et pathologique, *Sang* **11** 804, 1937.

44 In pernicious anemia megaloblasts appear in the marrow, while in cryptogenic hypochromic anemia, macroblasts are present and the marrow is hyperplastic. Secondary anemias are characterized by normoblastosis, in polycythemia, by hypererythroblastosis and a megakaryocytosis, in leukemia, by leukoblastosis, in agranulocytoses of different types, by aplasia or hypoplasia of the granulocytes, with or without change in the other elements, in cancerous conditions, by hyperplasia of neoplastic tissue, and in Hodgkin's disease, by an increase in plasmocytes, monocytes, eosinophils and large endothelial cells.

In bone marrow of patients with Bright's disease Alexeieff⁴⁴⁹ found a feeble erythroblastic regeneration, and the normal normoblast-granulocyte ratio of 1:5 was changed to 1:10. For 16 patients the erythrocyte counts of the peripheral blood varied from 2,200,000 to 4,950,000 per cubic millimeter and the leukocytes from 4,000 to 9,600. Alexeieff attributed the anemia to intoxication of the bone marrow with nitrogenous products, proportional to the duration of the disease but not the degree of azotemia. Leukocytosis (mercury bichloride poisoning) is an evidence of bone marrow regeneration. Hemorrhage is not due to thrombopenia, and the megakaryocytes and platelets are not affected. The variations in the nonprotein nitrogen content of the blood and of the bone marrow are comparable. In mercury bichloride poisoning in man and dogs the nonprotein nitrogen content of the marrow is elevated above that of the blood, differing in this respect from most of the other nephritides.

Domarus⁴⁵⁰ cited 2 cases in which conclusions drawn from sternal puncture material were exactly opposed to the actual condition in the marrow. In the first case the diagnosis was active regeneration, when in reality the bone marrow was aplastic, in the second case a false diagnosis of aplastic anemia was made.

Kingery, Osgood and Illge⁴⁵¹ found sternal puncture a useful method in the diagnosis of leukemia cutis and in the differentiation of the lymphoblastoma. Weller⁴⁵² also found this technic useful. He used a spinal puncture needle, 18 gage and 3 inches (7.6 cm) long, and withdrew a bit of marrow tissue, from which films were made.

449 Alexeieff, G. La moelle osseuse des brightiques. Contribution sur l'étude de l'hématopoïèse et définition de l'azote non protéique dans la moelle osseuse des brightiques, *Sang* **11** 972, 1937.

450 von Domarus, A. Ueber Irrtumer bei Auswertung der Sternalpunktion, *Klin. Wchnschr.* **16** 557, 1937.

451 Kingery, L. B., Osgood, E. F., and Illge, A. H. Sternal Puncture. A Diagnostic Aid in Leukaemia Cutis, a Possible Aid in Differentiating the Lymphoblastomas, *Arch. Dermat. & Syph.* **35** 910 (May) 1937.

452 Weller, G. L., Jr. Bone Marrow Findings in the Diagnosis of Certain Blood Dyscrasias, *M. Ann. District of Columbia* **6** 253, 1937.

Osgood and Brownlee ⁴⁵³ developed a method of tissue culture for the study of bone marrow aspirated by sternal puncture. The material is grown in a synthetic saline solution containing dextrose. Other substances were added. The number of mitotic figures increased from forty to sixty times the number in the original marrow. With this method Osgood ⁴⁵⁴ found that polymorphonuclear neutrophils survived in the solution for sixty-one (forty-eight to ninety) hours, eosinophils, eight to twelve days, and basophils, twelve to fifteen days.

In vitro studies of human bone marrow were made by Weitzmann and Posern ⁴⁵⁵

Dameshek and Valentine ³⁷ studied the sternal bone marrow of 20 patients with pernicious anemia at various stages of the disease. Tissues fixed in Zenker's solution (prepared according to the original formula, with acetic acid) and direct films were used, the latter being more valuable for cytologic data. The earlier work of Isaacs ⁴⁵⁶ was confirmed. The changes in the bone marrow were those of panmyelophthisis rather than a disease of red blood cells only.

In cases of tuberculosis Engelbreth-Holm ⁴⁵⁷ noted that splenomegaly, anemia and leukopenia developed because of a restriction of the maturing or delivering of the cells from the bone marrow and not from a decrease in cell production.

Lorando ⁴⁵⁸ found sternal puncture of value in the diagnosis of leishmaniasis. He noted that splenic puncture was not without danger. Giraud and Gaubert ⁴⁵⁹ said they preferred tibial puncture, especially for children. In kala-azar a positive diagnosis was made in 15 of 22 cases by means of this method. In 7 cases tibial puncture gave "nega-

453 Osgood, E. E., and Brownlee, I. E. Culture of Human Marrow. Details of a Simple Method, *J. A. M. A.* **108** 1793 (May 22) 1937.

454 Osgood, E. E. Culture of Human Marrow. Length of Life of the Neutrophils, Eosinophils, and Basophils of Normal Blood as Determined by Comparative Cultures of Blood and Sternal Marrow from Healthy Persons, *J. A. M. A.* **109** 933 (Sept 18) 1937.

455 Weitzmann, G., and Posern, E. Ueber das Wachstum menschlichen Knochenmarks in vitro, *Virchows Arch. f. path. Anat.* **299** 458, 1937.

456 Isaacs, R. The Bone Marrow Changes (Quantitative) in Patients with Pernicious Anemia During the Period of "Reticulocyte Response," *Tr. A. Am. Physicians* **50** 249, 1935.

457 Engelbreth-Holm, J. Tuberculous Splenomegaly and Splenogenic Inhibition of Bone Marrow Function, *Bibliot. f. læger* **129** 17, 1937.

458 Lorando, N. La ponction sternale, methode de choix pour la recherche des leishmanies, *Bull. et mem. Soc. med. d. hôp. de Paris* **53** 314, 1937.

459 Giraud, P., and Gaubert. Valeur de la ponction de la moelle osseuse pour le diagnostic du kala-azar mediterraneen (d'apres les resultats de 22 ponctions du tibia), *Bull. et mem. Soc. med. d. hôp. de Paris* **53** 336, 1937.

tive" results, while splenic puncture gave positive results. In 1 case splenic puncture gave a negative result and tibial aspiration a positive result.

Huddleson and Munger⁴⁶⁰ studied the phagocytic activity of the cells of the marrow aspirated from the cavity of the femur of normal guinea pigs and of those immunized to *Brucella* and of cells from a patient with chronic myelogenous leukemia. While the cells from normal marrow did not ingest the bacteria mixed with them, cells or serum from an immune animal stimulated active phagocytosis. Leukemic cells did not phagocytose bacteria, but when human serum containing immune opsonins was added, the mature polymorphonuclear neutrophils and the stab forms ingested bacteria, although the cells of younger stages were inactive.

Brewer⁴⁶¹ found that bone marrow had a high content of the potassium isotope⁴¹.

In tissue cultures of spleen and of bone marrow Yagi⁴⁶² noted inhibition of growth when estrogenic substance was added, but the growth was stimulated when androgen was used. The reverse was true for certain other tissues. Corn oil and olive oil stimulated the growth of hemopoietic organs to the greatest extent of the ten vegetable oils used, the next most effective being oils of rapeseed, sesame and camellia.

In cultures of bone marrow Larionov⁴⁶³ found that toluene and xylene were more strongly toxic than benzene. Ether and acetone killed the bone marrow cells only in high concentration. Benzene was toxic to leukocytes *in vitro*.

HEMATOLOGIC TECHNIC

Erythrocyte and hemoglobin values for newborn infants were determined by Andersen and Ortmann⁴⁶⁴. Wide variations among presumably normal subjects were found. In general, the blood picture was characterized by macrocytosis and a high color index. They suggested the usefulness of determining the total quantity of blood in the newborn.

460 Huddleson, I. F., and Munger, M. Phagocytic Activity of Bone Marrow Cells, *Proc Soc Exper Biol & Med* **35** 27, 1937.

461 Brewer, A. K. Abundance Ratio of the Isotopes of Potassium in Animal Tissues, *J Am Chem Soc* **59** 869, 1937.

462 Yagi, M. Ueber die Einwirkungen des Ovahormons und des Enarmons auf die Entwicklung der Organgewebe des Kaninchens *in Vitro* gezuchtet, *Sci-I-Kai M J (Abstr Sect)* **56** 14, 1937.

463 Larionov, L. T. Weitere Studien über die Wirkung der aromatischen Kohlenwasserstoffe und anderer Narkotika auf die Gewebekulturen, *Arch f exper Zellforsch* **19** 16, 1936.

464 Andersen, B., and Ortmann, G. On the Number of Erythrocytes and the Content of Haemoglobin in the Blood of New-Born Children, *Acta med Scandinav* **93** 410, 1937.

Dhar ⁴⁶⁵ found the average hemoglobin value for native women of India to be 11.47 Gm per hundred cubic centimeters, the erythrocyte count, 3,730,000 per cubic millimeter, the corrected color index 0.99, and the mean cell diameter 7 microns. His observations of lower normal blood values for Indian women than have been reported for the female population of Europe and America are in agreement with the findings of Napier and Das Gupta ¹⁴⁵. From his studies of the blood of normal Filipinos, Navarro ⁴⁶⁶ likewise found in both men and women slightly smaller erythrocytes, which contained less hemoglobin than those of healthy Americans. Biedenkopf ⁴⁶⁷ determined the hemoglobin and erythrocyte values, the mean corpuscular hemoglobin value, the diameter and area of the erythrocytes and the hemoglobin content per square micron of surface for 40 elderly men and women. He found that the sex differences in regard to red blood cell count and hemoglobin level were less marked in subjects over 60 years of age than in younger persons. Duhère and Adant ⁴⁶⁸ found that with an approximation of 5 to 6 per cent, they could deduce from the hematocrit percental volume of the erythrocytes the concentration of iron and of hemoglobin, the oxygen capacity and, in many cases, the red blood cell count. However, in comment, it should be pointed out that such deductions are valid only in the presence of erythrocytes of normal size and of a normal hemoglobin content. The mean corpuscular weight of the red blood cells of healthy men and women was determined by Isaacs, Bethell and Kyer ⁴⁶⁹. For men the average value was found to be 73.6 micromicrograms, for women, 74.12 micromicrograms. There appeared to be no simple correlation between hemoglobin weight and total cell weight.

Weld and Woodward ⁴⁷⁰ suggested a modification of the method of determining the blood volume with congo red dye. Small amounts

465 Dhar, J. Normal Hematological Standards in Indian Women, *Folia haemat* **57** 78, 1937.

466 Navarro, R. J. Hematology in Filipinos. Normal Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, and Mean Corpuscular Hemoglobin Concentration, the Various Normal Blood Indexes, *J. Philippine Islands M. A.* **17** 611, 1937.

467 Biedenkopf, H. Das Blut des Menschen, mit neueren Methoden untersucht, absolute Hamoglobinbestimmungen Erythrozytenzahlungen und Erythrozytenmessungen bei 40 alten Männern und Frauen zur Ermittlung des Hamoglobingehalts eines Erythrozyten und des Hamoglobins je μ^2 Oberfläche des Erythrozyten, *Ztschr. f. Biol.* **97** 445, 1936.

468 Duhère, W. L., and Adant, M. Relation entre le volume globulaire et la concentration en fer. Signification du chiffre de l'hématocrite, *Bull. Soc. chim. biol.* **18** 1589, 1936.

469 Isaacs, R., Bethell, F. H., and Kyer, J. L. The Weight of Red Blood Cells in Health and Anemia, *Univ. Hosp. Bull., Ann Arbor* **3** 85, 1937.

470 Weld, C. B., and Woodward, H. E. Note on Blood Volume Determinations, *J. Lab. & Clin. Med.* **22** 410, 1937.

of hydrogen peroxide are added to both the standard and the unknown solution, thus bleaching out hemoglobin resulting from hemolysis. The procedure is especially valuable in determinations of the blood volume of dogs, in which hemolysis is likely to be a troublesome factor.

The mean diameter of erythrocytes was determined by Schalm,⁴⁷¹ using different instruments for the measurement of diffraction rings. Most accurate determinations of the size of the red blood cells were obtained with Pijper's instrument, and by this method the normal mean diameter was found to be 7.8 microns. Values were reported for mean erythrocyte diameter in cases of hepatic disease and obstructive jaundice. Freerksen⁴⁷² found that the size of the red blood cells in health and in disease conditions is remarkably constant and that it depends on the size of the antecedent normoblasts. He concluded that changes in the size of the erythrocytes occurring in various diseases of the erythropoietic system must always be considered in conjunction with quantitative changes in the marrow.

Tocantins⁴⁷³ reviewed the subject of the technologic study of blood platelets. He described many methods for the enumeration of platelets and their morphologic study. A technic was given for the study of platelets and megakaryocytes in sections of fixed tissue. The volumetric measurement of platelets was discussed, as well as methods for the isolation of platelets from the blood. He also described the preparation and testing of antiplatelet serum. He⁴⁷⁴ found that the number of platelets in arterial and venous blood was significantly higher in winter than in spring but that no such difference occurred in cutaneous blood. In winter the platelet count was found to be highest in arterial blood, but counts made in spring on blood from the arteries, veins and cutaneous vessels were essentially the same. He found no statistically significant seasonal variations in red blood cell counts.

A technic for the determination of platelet volume was described by Olef.⁴⁷⁵ The principle of the method depends on immediate dilution of the venous blood with a platelet-preserving solution, rapid isolation of platelets by centrifugation and measurement of volume by subsequent centrifugation of the suspension of platelets in a thrombocytocrit pipet. The mean total platelet volume for 31 normal adults was 0.33 volumes.

471 Schalm, L. Measurement of the Mean Diameter of Red Blood Cells, *Nederl tijdschr v geneesk* **81** 5786, 1937.

472 Freerksen, E. Das Problem der Erythrocytengrosse—Eine anatomische Frage? *Klin Wchnschr* **16** 1238, 1937.

473 Tocantins, L. M. Technical Methods for the Study of Blood Platelets *Arch Path* **23** 850 (June) 1937.

474 Tocantins, L. M. Seasonal Variations in the Number of Platelets in the Arterial, Venous and Cutaneous Blood in Man, *Am J Physiol* **119** 439, 1937.

475 Olef, I. Determination of Platelet Volume, *J Lab & Clin Med* **23** 166, 1937.

per cent, with a range of 0.26 to 0.44 per cent. The mean individual platelet volume for the group was 7.3 cubic microns. The author concluded that the determination of the volume of packed platelets is a useful hematologic procedure but that it should not be used as a substitute for platelet enumeration, because of a lack of absolute parallelism between the volume and the total count, attributable to variations in the fragility and in the size of the thrombocytes.

The usefulness of a simple test for the estimation of erythrocyte sedimentation was discussed by Bannick, Gregg and Guernsey⁴⁷⁶. They found a threefold application of the test to clinical problems: (1) detection of disease, (2) measurement of activity and progress of such diseases as tuberculosis, pelvic inflammatory conditions, acute cholecystitis, rheumatic fever, infectious arthritis, pneumonia and other thoracic infections and suppurations, Hodgkin's disease, acute febrile illnesses and acute coronary thrombosis, and (3) assistance in differential diagnosis. Brooks⁴⁷⁷ and Dorfman and Brooks⁴⁷⁸ described a new micropipet for measurement of the sedimentation rate and studied the effects of temperature, inclination of the tube and delay in carrying out the test after removal of the blood sample. Frimberger⁴⁷⁹ found an inverse relation between the minimum sedimentation rate and the hemoglobin value, the erythrocyte count and the color index when these determinations were below normal levels. Extensive experimental and clinical studies of the sedimentation rate, made chiefly on patients with pulmonary tuberculosis, were reported by Carez and Wynants⁴⁸⁰. They concluded that both the time curve and the time required for the red blood cells to fall a given distance should be taken into consideration in determining the rate of sedimentation, and they presented a mathematical expression for the combined readings. Their article included a partial review of the literature. Volk⁴⁸¹ reported the results of 1,000 determinations of the sedimentation rate made for patients with pulmonary tuberculosis. The Cutler method was employed in this study. He found

476 Bannick, E. G., Gregg, R. O., and Guernsey, C. M. The Erythrocyte Sedimentation Rate. The Adequacy of a Single Test and Its Practical Application in Clinical Medicine, *J. A. M. A.* **109** 1257 (Oct. 16) 1937.

477 Brooks, C. New Micropipet for Sedimentation Measurement, *Am. J. M. Technol.* **3** 1, 1937.

478 Dorfman, R. I., and Brooks, C. The Accuracy of a New Technique for Measurement of Red Blood Corpuscle Sedimentation, *J. Lab. & Clin. Med.* **22** 510, 1937.

479 Frimberger, F. Das Minimalsediment des Blutes und seine Beziehungen zu Zahl und Hämoglobingehalt der Erythrocyten, *Klin. Wchnschr.* **16** 90, 1937.

480 Carez, C., and Wynants, J. H. New Method of Reading Sedimentation Rate, *Rev. de la tuberc.* **3** 774, 1937.

481 Volk, R. Red Cell Sedimentation in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **36** 567, 1937.

the test of especial value in measuring the activity of the disease in the presence of pneumothorax or thoracoplasty, roentgen findings frequently being limited to evidence of pulmonary collapse. Riseman and Brown¹⁸ studied changes in the sedimentation rate of patients with angina pectoris and coronary thrombosis. They found a moderate increase in rate in the former condition and much more marked acceleration in the latter, especially between the fourth and the twelfth day after the attack. They concluded that for two weeks after an acute onset the sedimentation rate may offer valuable aid in differentiating between angina pectoris and coronary thrombosis. It is not useful in the prognosis of an acute attack but is helpful in measuring progress during recovery.

482 Riseman, J. E. F., and Brown, M. G. Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, *Am J M Sc* **194** 392, 1937

News and Comment

International Congress on Rheumatic Diseases—At the International Congress on Rheumatic Diseases held at the University of Oxford, March 28 to 31, 1938, Dr Ralph Pemberton, of Philadelphia, was elected president, to succeed Dr R Fortescue Fox, of London, who did not wish to accept a new appointment as council member. At the urgent request of the members, the secretary and director of the International Advisory Bureau, Dr J van Breemen of Amsterdam, who had tendered his resignation, expressed his willingness to remain in office for the present. The other council members were re-elected. Prof J Rother, of Berlin, was given a seat on the council as representative for Germany.

A committee was appointed to collect statistics, to revise the by-laws and to reorganize the journal *Acta rheumatologica*.

The invitation of the American delegates to hold the next congress in New York in June 1940 was accepted. The official subjects to be discussed at that meeting will be (1) the role of infection in rheumatic diseases, (2) nutrition in rheumatism and (3) the social significance of orthopedic work in rheumatic diseases.

It was also resolved to hold a symposium on therapy in rheumatism and to furnish opportunities for the presentation of unscheduled papers.

American Congress of Physical Therapy and American Occupational Therapy Association—The seventeenth annual scientific and clinical session of the American Congress of Physical Therapy will be held cooperatively with the twenty-second annual convention of the American Occupational Therapy Association, Sept 12 to 15, 1938, at the Palmer House, Chicago. Preceding this session, from September 7 to 10, inclusive, the congress will conduct an intensive seminar on physical therapy for physicians and technicians. The program of the convention proper will include numerous special features, and a variety of papers and addresses, clinical conferences, round table talks and extensive scientific and technical exhibits are scheduled.

Information concerning the convention and the seminar may be obtained by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Book Reviews

Textbook of Diagnostic Roentgenology By Lewis J. Friedman, M.D.,
Director, Roentgen-Ray Department of the Bellevue Hospital Price, \$10
Pp 623, with 638 illustrations New York D. Appleton-Century Company,
Inc., 1937

This book consists of thirty-four chapters, which are divided among six clearly demarcated sections. In the first section the author considers certain of the fundamental principles of the physics of the roentgen ray, describes the technic of fluoroscopy and outlines standard methods for obtaining satisfactory roentgenograms. The succeeding sections of the volume are devoted, respectively, to the roentgenographic aspects of diseases of the osseous system, the respiratory system, the cardiovascular system, the alimentary tract and the genito-urinary tract, including in the latter field diseases of the uterus, adnexa and female pelvis and roentgenographic pelvimetry.

The book as a whole contains a wealth of sound and practical information. For the most part the descriptions of the various subjects under discussion are clear, and the illustrations are adequate, a few illustrations, to be sure, are poorly reproduced. There are occasional line drawings which are well described. There are concise, well written summaries describing the newer roentgenographic procedures, such as the diagnostic use of iodized oil, ventriculography, encephalography, myelography, bronchography, kymography, cholangiography, urography, salpingo-hysterography, and methods of visualization of the spleen and liver. These are especially interesting not only to the roentgenologist but also to the internist, because these newly developed methods are indicative of the trend this science has taken in recent years.

In each of the chapters many useful points of differential diagnosis are presented, and diseases of the various systems are discussed in a manner which is helpful to any one in practice. Thus the book is of interest to the general reader as well as to the specialist.

It is, of course, to be expected, because the book has attempted to cover so large a field, that many items would be briefly treated and some even omitted. No reference is made, for example, to the roentgenographic findings in cases of sprue and steatorrhea. Adenoma of the gallbladder is dismissed with one sentence. These gaps in a measure are compensated for by a well selected bibliography at the end of each chapter.

The allotment of space for the subject matter has been wisely handled. The book has been well written and is one that any physician can read with profit and find valuable as a work of reference. It is well adapted for teaching purposes. It clearly demonstrates the tremendous present-day value of roentgenography in the diagnosis of various diseases. On the whole, this new textbook can be heartily recommended.

Pathology of the Central Nervous System By Cyril B. Courville, M.D.,
Professor of Neurology and Psychiatry, College of Medical Evangelists, and
Director, Cajal Laboratory of Neuropathology, Los Angeles County Hospital
Price, \$5.75 Pp 344, with 200 illustrations Mountain View, California
Pacific Press Publishing Association, 1937

This new textbook has been written for medical students at their request and for this reason has been kept simple. Because of its simplicity it will appeal to many general readers, particularly those interested in the nervous system but a little fearful of its intricacies.

The author, being a pathologist, avoids as best he can the attachment of personal names to the different clinical syndromes that are encountered in the field of

clinical neurology Rather, he wishes to have his students learn to make clinical diagnoses on a pathologicophysiology basis, and he attempts to show how this may be done in a logical manner

His method of approach is pleasant He claims that for a proper understanding of diseases of the nervous system the life history of each lesion, as well as its peculiar predilections for certain regions of the brain or spinal cord, is of vital importance and that knowledge of the pathogenesis of the various diseases of the nervous system often gives a clue as to the nature of their early manifestations He attempts to lay the necessary foundation for such a point of view by a painstaking clinicopathologic analysis of the material that has passed through his laboratory, comprising a series of fifteen thousand autopsies

In this analysis especial emphasis is laid on the stage of development of the lesions under consideration which have been shown in his cases, on their gross morphologic character and on their ultimate effect on the nervous system Thus, relatively little space has been given to a description of minute histologic alterations, and a great deal has been given to gross pathologic and clinical description

The subject matter is divided in an orthodox manner The congenital anomalies, the diseases of the intracranial blood vessels, the infectious diseases, traumas, the intoxications, the degenerative diseases of unknown origin, like multiple sclerosis, and the tumors, each receives appropriate discussion

The entire volume makes interesting reading It is well indexed, with a good bibliography for reference work It is beautifully illustrated with photographs and easily comprehended diagrams It contains many useful clinical aphorisms On the whole, this new volume on the pathology of the central nervous system is well worth acquiring

Some Fundamental Aspects of the Cancer Problem Symposium Sponsored by the Section on Medical Sciences of the American Association for the Advancement of Science Edited by Henry Baldwin Ward Price, \$2.50 Pp 248, with illustrations and tables New York The Science Press, 1937

In the last days of 1936 the Section on Medical Sciences of the American Association for the Advancement of Science held a symposium on cancer at Atlantic City, N J The papers which were presented have now been assembled in book form under the editorship of Dr Ward The result is an impressive volume

The book is made up of thirty-one articles, short for the most part, well written and well illustrated with the necessary tables and graphs to make for clarity Cancer is considered from four points of view heredity, agents that may stimulate or inhibit tumorous growths, the metabolism of cancerous tissue and irradiation and, finally, by general discussion The papers dealing with these subjects are grouped together as informatively as possible Each paper is written by an authority in the particular field under discussion

The student of cancer will be glad to have so complete and polished a record of this symposium Especially, however, medical students and physicians should be encouraged to read this book For if, as Dr Dublin predicts, during the next twenty-five years in this country the present annual toll of 150,000 lives as a result of cancer is doubled, cancer and its problems must continue to be of increasing interest to all members of the profession Here is an excellent opportunity for physicians and students to learn how cancer is at present being investigated and to gain an inkling of the new lines of attack that are likely to be developed in the immediate future

Der Blutdruck des Menschen By Eskil Kylv, M D Price, 24 marks Pp 322, with 22 illustrations Dresden Theodor Steinkopff, 1937

This book represents 261 pages of discussion on the blood pressures of man, including not only the arterial but the capillary and the venous pressure as well Methods for determinations of the pressure in each class of vessels are described,

criticized and evaluated. The physiology of the regulation of blood pressure is detailed. Central, reflex, and hormonal control are given adequate consideration. Normal regulation is followed by pathologic physiology, leading to a consideration of both hypertension and hypotension. Included are such special cases as the Cushing syndrome, diabetes, adrenal tumors, pregnancy, essential and postural hypotension and Addison's disease.

Although the work is highly colored by German thought and ideas, the literature reviewed is world wide, a fact well reflected in the text itself. One will find in it little regarding specific directions for the handling and treatment of the patient. However, it will supply the physician with much recent knowledge regarding normal and pathologic physiology, which is so essential to the proper understanding of the nature of blood pressure control and consequently to the rational management of the patient.

Le eritremie. By G. di Guglielmo. Pp. 23. Pavia: Tipografia Gia Cooperativa, 1936.

This paper is an attempt to classify the proliferative disorders of the erythropoietic system logically. The preferred term for the group is erythremic myelosis. The subdivisions, in order of decreasing anaplasia of the erythropoietic tissue, are as follows:

- 1 Very acute erythremic myelosis of the newborn (erythroblastosis foetalis)
- 2 Acute erythremic myelosis (acute erythroblastic anemia)
- 3 Chronic erythremic myelosis (Cooley's erythroblastic anemia)
- 4 Chronic erythremic myelosis, Vaquez type (polycythaemia vera). Intergradations between these forms and leukemic myeloses of comparable severity are described and named. (In the discussion which followed the presentation of the paper the author suggested including this fourth form.)

The syndromes discussed appear to be more common in Italy than in this country. The discovery and the recognition of the rarer types, especially the leukemic and erythremic combinations, are praiseworthy, and the logical classification offered is a credit to Italian hematology.

The Roentgenologist in Court. By Samuel Wright Donaldson, M.D. Price, \$4. Pp. 230. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This is an interesting book. The author believes that most physicians know far too little regarding legal matters, and he here attempts to tell something of the mysteries of the law and how they may affect physicians.

The subject matter has been divided into fourteen chapters. These chapters deal with such broad legal topics as malpractice, testimony and contracts and have, as would be judged from the title of the volume, a good deal to say about the roentgenologist and his legal position.

The author has quoted a great number of cases to show how legal opinion regarding various phases of medical work has become established. So many legal case reports make the reading a little difficult for one unfamiliar with legal phraseology. However, the book as a whole makes an excellent work of reference. There is no doubt, as the author infers, that physicians are woefully ignorant of legal matters. This book at least puts them in the way of acquiring a modicum of medicolegal education.

Investigations into the Epidemiology of Epidemic Dropsy. By R. B. Lal, S. C. Roy and S. C. Ghosal. Pp. 97. Calcutta: Thacker, Spink & Co., 1937.

This paper, a reprinting of five articles from the *Indian Journal of Medical Research*, is a competent modern study of a disease of peculiar interest to public health officers. The syndrome of epidemic dropsy has been recognized in eastern India since 1877. There have been frequent outbreaks, resulting in as many as 1,575 deaths, although most of them have involved the relatively few inhabitants

of small Bengalese villages. Earlier epidemiologists attributed the outbreaks to bacterial toxins generated in infected rice. The present writers appear to have eliminated rice as the poisoning agent and have demonstrated convincingly that certain pressings of mustard oil (the chief food fat of the victims) are responsible for the disease. Unfortunately the nature of the toxic substance is not disclosed in this paper, but further researches are promised.

Clinical Studies of Tributary Thrombosis in the Central Retinal Vein By Viggo A. Jensen. Copenhagen: Levin & Munksgaard, 1936.

This work offers a complete study of the vascular system of the eye as a preliminary to the main theme, tributary thrombosis of the central retinal vein.

The author attempts to prove that there is a system in the apparently irregular branching of the retinal vessels, and he feels that he has established certain typical variations in the known course of the vessels.

The second section of this treatise deals with clinical studies of cases of tributary thrombosis. The ophthalmoscopic picture is described and correlated with the anatomic studies reported in the first section of the work.

Studies of the visual fields in the course of the disease and many drawings illustrating the picture of the fundus in cases of tributary thrombosis accompany the text. The fifty-four patients studied were followed through to the ultimate conclusion.

The Endocrines in Theory and Practice Republished from the *British Medical Journal*. Price, 9s. Pp. 278. London: H. K. Lewis & Co., Ltd., 1937.

This volume is a collection of papers reprinted from the *British Medical Journal* and designed to familiarize the reader with the present status of endocrinology. The subject is discussed from a practical standpoint, and theoretical considerations are eliminated so far as possible.

The pituitary body, the thyroid gland, the adrenal glands and the gonads are discussed at length. The thymus, the pineal body and the parathyroid glands receive somewhat less attention.

Clinical considerations of diagnosis and treatment are given a prominent place.

A difference in the British and in the American point of view is shown in certain places. This is particularly evident in the discussion of the etiology of goiter and in the treatment of hyperthyroidism.

The whole book is sound and conservative, and a place in the literature of endocrinology is well merited.

Diseases of the Nervous System in Infancy, Childhood and Adolescence

By Frank R. Ford, M.D. Price, \$8.50. Pp. 953, with 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

As it is well printed and beautifully and profusely illustrated, one immediately has a sense of pleasure on opening this book. Dr. Ford has dealt with his subject thoroughly. Of special value are the discussions of the neurologic conditions of childhood. One wishes that he had devoted more space to these, since there is otherwise a good deal of material which is readily available in general medical and neurologic textbooks. Especially valuable are the references, conveniently placed after each section. The abstracts of individual cases make a difficult subject more vivid and comprehensible.

La thrombose de l'artère bronchique, cause de dilatation bronchique chronique de l'adulte By J. M. Lemoine, M.D. Price, 30 francs. Pp. 189, with 27 illustrations. Paris: E. Le François, 1936.

In this brief monograph the author sustains the thesis that bronchial dilatation is due to thrombosis of the bronchial artery. While one may not agree with the conclusions, one must admit that a good deal of interesting material has been assembled.

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